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(21) International Application Number: PCT/US99/27946 (22) International Filing Date: 17 December 1999 (17.12.99) (30) Priority Data: 60/113,955 23 December 1998 (23.12.98) US (71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): KELLER, Bradley, T. [US/US]; 1780 Canyon View Court, Chesterfield, MO 63017 (US). REITZ, David, B. [US/US]; 14814 Pleas- ant Ridge Court, Chesterfield, MO 63017 (US). SCHUH, Joseph, R. [US/US]; 2055 Rurline, St. Louis, MO 63146 (US). SIKORSKI, James, A. [US/US]; 2313 East Royal Court, St. Louis, MO 63131 (US). TREMONT, Samuel, J. [US/US]; 729 Berquest Drive, St. Louis, MO 63011 (US). LAPPE, Rodney, W. [US/US]; 1569 Wildhorse Parkway Drive, Chesterfield, MO 63005 (US). (74) Agents: WILLIAMS, Roger, A. et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: COMBINATIONS FOR CARDIOVASCULAR INDICATIONS			
(57) Abstract The present invention provides combinations of cardiovascular therapeutic compounds for the prophylaxis or treatment of cardiovascular disease including hypercholesterolemia and atherosclerosis. Combinations disclosed include an ileal bile acid transport inhibitor combined with a cholesteryl ester transport protein (CETP) inhibitor, a fibric acid derivative, a nicotinic acid derivative, a microsomal triglyceride transfer protein inhibitor, a cholesterol absorption antagonist, a phytosterol, a statin, an antihypertensive agent, or others. Further combinations include a CETP inhibitor with a fibric acid derivative, a nicotinic acid derivative, a bile acid sequestrant, a microsomal triglyceride transfer protein inhibitor, a cholesterol absorption antagonist, or others.			

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Combinations for Cardiovascular Indications

This application claims priority of U.S. provisional application Ser. No. 60/113,955 filed Dec. 23, 1998.

5

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to methods of treating
10 cardiovascular diseases, and specifically relates to
combinations of compounds, compositions, and methods for
their use in medicine, particularly in the prophylaxis and
treatment of hyperlipidemic conditions such as are
associated with atherosclerosis, hypercholesterolemia, and
15 other factors in coronary artery disease in mammals
including hypertension. More particularly, the invention
relates to ileal bile acid transporter (IBAT) inhibitors,
cholesteryl ester transfer protein (CETP) activity
inhibitors, fibric acid derivatives (fibrates), nicotinic
20 acid derivatives, microsomal triglyceride transfer protein
(MTP) inhibitors, cholesterol absorption antagonists,
stanols, phytosterols, or antihypertensive agents.

Description of Related Art

25 It is well-settled that hyperlipidemic conditions
associated with elevated concentrations of total
cholesterol and low-density lipoprotein (LDL)
cholesterol are major risk factors for coronary heart
disease and particularly atherosclerosis. Numerous
30 studies have demonstrated that a low plasma
concentration of high density lipoprotein (HDL)
cholesterol is a powerful risk factor for the
development of atherosclerosis (Barter and Rye,
Atherosclerosis, 121, 1-12 (1996)). HDL is one of the

2

major classes of lipoproteins that function in the transport of lipids through the blood. The major lipids found associated with HDL include cholesterol, cholesteryl ester, triglycerides, phospholipids and fatty acids. The other classes of lipoproteins found in the blood are low density lipoprotein (LDL), intermediate density lipoprotein (IDL), and very low density lipoprotein (VLDL). Since low levels of HDL cholesterol increase the risk of atherosclerosis, methods for elevating plasma HDL cholesterol would be therapeutically beneficial for the treatment of atherosclerosis and other diseases associated with accumulation of lipid in the blood vessels. These diseases include, but are not limited to, coronary heart disease, peripheral vascular disease, and stroke.

Atherosclerosis underlies most coronary artery disease (CAD), a major cause of morbidity and mortality in modern society. High LDL cholesterol (above about 180 mg/dl) and low HDL cholesterol (below 35 mg/dl) have been shown to be important contributors to the development of atherosclerosis. Other diseases or risk factors, such as peripheral vascular disease, stroke, and hypercholesterolaemia are negatively affected by adverse HDL/LDL ratios.

Interfering with the recirculation of bile acids from the lumen of the intestinal tract is found to reduce the levels of serum cholesterol in a causal relationship. Epidemiological data has accumulated which indicates such reduction leads to an improvement in the disease state of atherosclerosis. Stedronsky, in "Interaction of bile acids and cholesterol with nonsystemic agents having hypocholesterolemic properties," Biochimica et Biophysica Acta, 1210, 255-287 (1994) discusses the biochemistry,

physiology and known active agents surrounding bile acids and cholesterol.

Transient pathophysiologic alterations are shown to be consistent with interruption of the enterohepatic circulation of bile acids in humans with an inherited lack of IBAT activity, as reported by Heubi, J.E., et al. See "Primary Bile Acid Malabsorption: Defective in Vitro Ileal Active Bile Acid Transport", Gastroenterology, 83, 804-11 (1982).

In another approach to the reduction of recirculation of bile acids, the ileal bile acid transport system is a putative pharmaceutical target for the treatment of hypercholesterolemia based on an interruption of the enterohepatic circulation with specific transport inhibitors (Kramer, et al., "Intestinal Bile Acid Absorption" The Journal of Biological Chemistry, 268 (24), 18035-46 (1993).

In several individual patent applications, Hoechst Aktiengesellschaft discloses polymers of various naturally occurring constituents of the enterohepatic circulation system and their derivatives, including bile acid, which inhibit the physiological bile acid transport with the goal of reducing the LDL cholesterol level sufficiently to be effective as pharmaceuticals and, in particular for use as hypocholesterolemic agents. The individual Hoechst patent applications which disclose such bile acid transport inhibiting compounds are each separately listed below.

- R1. Canadian Patent Application No. 2,025,294.
- R2. Canadian Patent Application No. 2,078,588.
- R3. Canadian Patent Application No. 2,085,782.
- R4. Canadian Patent Application No. 2,085,830.
- R5. EP Application No. 0 379 161.

R6. EP Application No. 0 549 967.

R7. EP Application No. 0 559 064.

R8. EP Application No. 0 563 731.

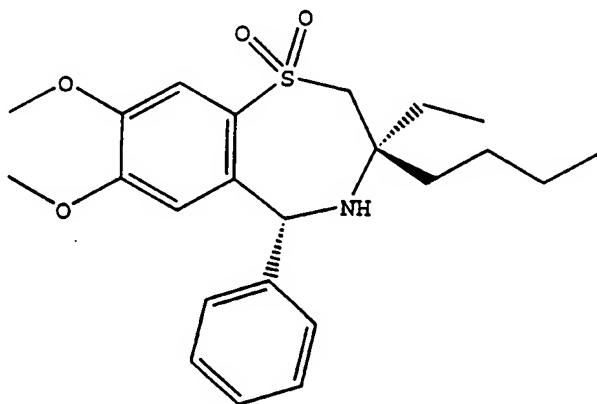
5 Selected benzothiepinines are disclosed in world patent application number WO 93/321146 for numerous uses including fatty acid metabolism and coronary vascular diseases.

Other selected benzothiepinines are known for use as
10 hypolipaeamic and hypocholesterolaemic agents, especially for the treatment or prevention of atherosclerosis as disclosed in application No. EP 508425. A French patent application, FR 2661676 discloses additional benzothiepinines for use as hypolipaeamic and
15 hypocholesterolaemic agents. Furthermore, patent application no. WO 92/18462 lists other benzothiepinines for use as hypolipaeamic and hypocholesterolaemic agents. U.S. Patent No. 5,994,391 (Lee et al.) Each of the benzothiepinine hypolipaeamic and hypocholesterolaemic agents
20 described in these individual patent applications is limited by an amide bonded to the carbon adjacent the phenyl ring of the fused bicyclobenzothiepinine ring.

Further benzothiepinines useful for the treatment of hypercholesterolemia and hyperlipidemia are disclosed in
25 patent application no. PCT/US95/10863. More benzothiepinines useful for the prophylaxis and treatment of hypercholesterolemia and hyperlipidemia as well as pharmaceutical compositions of such benzothiepinines are described in PCT/US97/04076. Still further benzothiepinines
30 and compositions thereof useful for the prophylaxis and treatment of hypercholesterolemia and hyperlipidemia are described in U.S. Application Serial No. 08/816,065.

In vitro bile acid transport inhibition is disclosed to correlate with hypolipidemic activity in The Wellcome

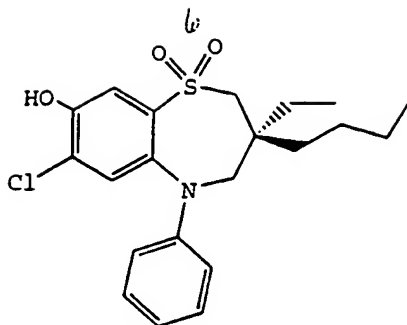
Foundation Limited disclosure⁵ of the Patent Application No. WO 93/16055 for "Hypolipidemic Benzothiazepine Compounds." That publication describes a number of hypolipidemic benzothiazepine compounds. Additional
5 hypolipidemic benzothiazepine compounds (particularly 2,3,4,5-tetrahydrobenzo-1-thi-4-azepine compounds) are disclosed in Patent Application No. WO 96/05188. A particularly useful benzothiazepine disclosed in WO 96/05188 is the compound of formula B-2. Further
10 hypolipidemic benzothiazepine compounds are described in Patent Application No. WO 96/16051.



B-2

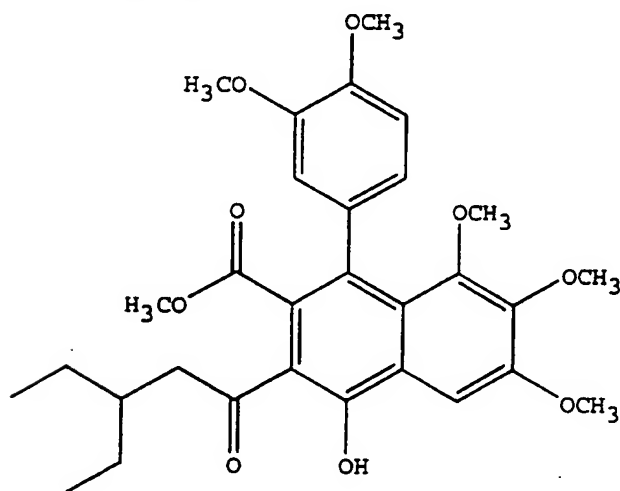
(3R, 5R)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-
7,8-dimethoxy-5-phenyl-1,4-benzothiazepine
1,1-dioxide

15 Other benzothiazepine compounds useful for control of cholesterol are 2,3,4,5-tetrahydrobenzo-1-thi-5-azepine IBAT inhibitor compounds described in PCT Patent Application No. WO 99/35135. Included in that description is the compound of formula B-7.



B-7

Further IBAT inhibitor compounds include a class of naphthalene IBAT inhibitor compounds, described by T. Ichihashi et al. in J. Pharmacol. Exp. Ther., 284(1), 43-50 (1998). In this class, S-8921 (methyl 1-(3,4-dimethoxyphenyl)-3-(3-ethylvaleryl)-4-hydroxy-6,7,8-trimethoxy-2-naphthoate) is particularly useful. The structure of S-8921 is shown in formula B-20. Further naphthalene compounds or lignin derivatives useful for the treatment or prophylaxis of hyperlipidemia or atherosclerosis are described in PCT Patent Application No. WO 94/24087.



B-20

Another class of lipid-lowering drug is an anti-obesity drug. An example of an antiobesity drug is orlistat. Orlistat is described in European Patent No. EP 0 129 748.

Inhibition of cholesteryl ester transfer protein (CETP) has been shown to effectively modify plasma HDL/LDL ratios, and is expected to check the progress and/or formation of certain cardiovascular diseases.

5 CETP is a plasma protein that facilitates the movement of cholesteryl esters and triglycerides between the various lipoproteins in the blood (Tall, J. Lipid Res., 34, 1255-74 (1993)). The movement of cholesteryl ester from HDL to LDL by CETP has the effect of lowering HDL

10 cholesterol. It therefore follows that inhibition of CETP should lead to elevation of plasma HDL cholesterol and lowering of plasma LDL cholesterol, thereby providing a therapeutically beneficial plasma lipid profile. Evidence of this effect is described in

15 McCarthy, Medicinal Res. Revs., 13, 139-59 (1993). Further evidence of this effect is described in Sitori, Pharmac. Ther., 67, 443-47 (1995)). This phenomenon was first demonstrated by Swenson et al., (J. Biol. Chem., 264, 14318 (1989)) with the use of a monoclonal antibody

20 that specifically inhibits CETP. In rabbits, the antibody caused an elevation of the plasma HDL cholesterol and a decrease in LDL cholesterol. Son et al. (Biochim. Biophys. Acta, 795, 743-480 (1984)) describe proteins from human plasma that inhibit CETP.

25 U.S. Patent 5,519,001, herein incorporated by reference, issued to Kushwaha et al., describes a 36 amino acid peptide derived from baboon apo C-1 that inhibits CETP activity. Cho et al. (Biochim. Biophys. Acta 1391, 133-144 (1998)) describe a peptide from hog plasma that

30 inhibits human CETP. Bonin et al. (J. Peptide Res., 51, 216-225 (1998)) disclose a decapeptide inhibitor of CETP. A depspeptide fungal metabolite is disclosed as a CETP inhibitor by Hedge et al. in Bioorg. Med. Chem. Lett., 8, 1277-80 (1998).

- There have been several reports of non-peptidic compounds that act as CETP inhibitors. Barrett et al. (J. Am. Chem. Soc., 118, 7863-63 (1996)) describe cyclopropane-containing CETP inhibitors. Further
- 5 cyclopropane-containing CETP inhibitors are described by Kuo et al. (J. Am. Chem. Soc., 117, 10629-34 (1995)). Pietzonka et al. (Bioorg. Med. Chem. Lett., 6, 1951-54 (1996)) describe phosphonate-containing analogs of cholesteryl ester as CETP inhibitors. Coval et al.
- 10 (Bioorg. Med. Chem. Lett., 5, 605-610 (1995)) describe Wiedendiol-A and -B, and related sesquiterpene compounds as CETP inhibitors. Lee et al. (J. Antibiotics, 49, 693-96 (1996)) describe CETP inhibitors derived from an insect fungus. Busch et al. (Lipids, 25, 216-220,
- 15 (1990)) describe cholesteryl acetyl bromide as a CETP inhibitor. Morton and Zilverman (J. Lipid Res., 35, 836-47 (1992)) describe that p-chloromercuriphenyl sulfonate, p-hydroxymercuribenzoate and ethyl mercurithiosalicylate inhibit CETP. Connolly et al.
- 20 (Biochem. Biophys. Res. Comm., 223, 42-47 (1996)) describe other cysteine modification reagents as CETP inhibitors. Xia et al. describe 1,3,5-triazines as CETP inhibitors (Bioorg. Med. Chem. Lett., 6, 919-22 (1996)). Bisgaier et al. (Lipids, 29, 811-8 (1994))
- 25 describe 4-phenyl-5-tridecyl-4H-1,2,4-triazole-thiol as a CETP inhibitor. Additional triazole CETP inhibitors are described in U.S. Patent Application Serial No. 09/153,360, herein incorporated by reference. Sikorski et al. disclosed further novel CETP inhibitors in PCT
- 30 Patent Application No. WO 99/14204.

Substituted 2-mercaptoaniline amide compounds can be used as CETP inhibitors and such therapeutic compounds are described by H. Shinkai et al. in PCT Patent Application No. WO 98/35937.

Some substituted heteroalkylamine compounds are known as CETP inhibitors. In European Patent Application No. 796846, Schmidt et al. describe 2-aryl-substituted pyridines as cholesterol ester transfer protein inhibitors useful as cardiovascular agents. One substituent at C₃ of the pyridine ring can be an hydroxyalkyl group. In European Patent Application No. 801060, Dow and Wright describe heterocyclic derivatives substituted with an aldehyde addition product of an alkylamine to afford 1-hydroxy-1-amines. These are reported to be β 3-adrenergic receptor agonists useful for treating diabetes and other disorders. In Great Britain Patent Application No. 2305665, Fisher et al. disclose 3-agonist secondary amino alcohol substituted pyridine derivatives useful for treating several disorders including cholesterol levels and atherosclerotic diseases. In European Patent Application No. 818448 (herein incorporated by reference), Schmidt et al. describe tetrahydroquinoline derivatives as cholesterol ester transfer protein inhibitors. European Patent Application No. 818197, Schmek et al. describe pyridines with fused heterocycles as cholesterol ester transfer protein inhibitors. Brandes et al. in German Patent Application No. 19627430 describe bicyclic condensed pyridine derivatives as cholesterol ester transfer protein inhibitors. In PCT Patent Application No. WO 9839299, Muller-Gliemann et al. describe quinoline derivatives as cholesteryl ester transfer protein inhibitors.

Polycyclic compounds that are useful as CETP inhibitors are also disclosed by A. Oomura et al. in Japanese Patent No. 10287662. For example, therapeutic compounds having the structures C-1 and C-8 were prepared by culturing *Penicillium* spp.

Cycloalkylpyridines useful as CETP inhibitors are disclosed by Schmidt et al. in European Patent No. EP 818448. For example, the therapeutic compound having the structure C-9 is disclosed as being particularly effective as a CETP inhibitor.

Substituted tetrahydronaphthalene compounds useful as CETP inhibitors are described in PCT Patent Application No. WO 9914174. Specifically described in that disclosure as a useful CETP inhibitor is (8S)-3-cyclopentyl-1-(4-fluorophenyl)-2-[(S)-fluoro(4-trifluoromethylphenyl)methyl]-8-hydroxy-6-spirocclobutyl-5,6,7,8-tetrahydronaphthalene.

Some 4-heteroaryl-tetrahydroquinolines useful as CETP inhibitors are described in PCT Patent Application No. WO 9914215. For example, that disclosure describes 3-(4-trifluoromethylbenzoyl)-5,6,7,8-tetrahydroquinolin-5-one as a useful CETP inhibitor.

In another approach to the reduction of total cholesterol, use is made of the understanding that HMG CoA reductase catalyzes the rate-limiting step in the biosynthesis of cholesterol (The Pharmacological Basis of Therapeutics, 9th ed., J.G. Hardman and L.E. Limberd, ed., McGraw-Hill, Inc., New York, pp. 884-888 (1996), herein incorporated by reference). HMG CoA reductase inhibitors (including the class of therapeutics commonly called "statins") reduce blood serum levels of LDL cholesterol by competitive inhibition of this biosynthetic step (M.S. Brown, et al., J. Biol. Chem, 253, 1121-28 (1978), herein incorporated by reference). Several statins have been developed or commercialized throughout the world. Mevastatin was among the first of the statins to be developed and it is described in U.S. Patent No. 3,983,140 (herein incorporated by reference). Lovastatin, another important HMG CoA reductase inhibitor, is described in

U.S. patent no. 4,231,938 (herein incorporated by reference). Simvastatin is described in U.S. patent no. 4,444,784 (herein incorporated by reference). Each of these HMG CoA reductase inhibitors contains a six-membered lactone function which apparently mimics the structure of HMG CoA in competition for the reductase. The HMG CoA reductase inhibitor class of cholesterol-lowering drugs is further exemplified by a group of drugs which contain 2,4-dihydroxyheptanoic acid functionalities rather than the lactone. One member of this group is pravastatin, described in U.S. patent no. 4,346,227 (herein incorporated by reference). Another HMG CoA reductase inhibitor which contains a 2,4-dihydroxyheptanoic acid group is fluvastatin, described in U.S. patent no. 5,354,772 (herein incorporated by reference). Warnings of side effects from use of HMG CoA reductase inhibitors include liver dysfunction, skeletal muscle myopathy, rhabdomyolysis, and acute renal failure. Some of these effects are exacerbated when HMG CoA reductase inhibitors are combined with fibrates or nicotinic acid.

Fibric acid derivatives comprise another class of drugs which have effects on lipoprotein levels. Among the first of these to be developed was clofibrate, disclosed in U.S. patent no. 3,262,850. Clofibrate is the ethyl ester of p-chlorophenoxyisobutyric acid. A widely used drug in this class is gemfibrozil, disclosed in U.S. patent no. 3,674,836. Gemfibrozil frequently is used to decrease triglyceride levels or increase HDL cholesterol concentrations (The Pharmacological Basis of Therapeutics, p. 893). Fenofibrate (U.S. patent no. 4,058,552) has an effect similar to that of gemfibrozil, but additionally decreases LDL levels. Ciprofibrate (U.S. patent no. 3,948,973) has similar effects to that of fenofibrate. Another drug in this class is bezafibrate (U.S. patent no.

3,781,328). Warnings of side¹² effects from use of fibric acid derivatives include gall bladder disease (cholelithiasis), rhabdomyolysis, and acute renal failure. Some of these effects are exacerbated when fibrates are
5 combined with HMG CoA reductase inhibitors.

Probucol is a powerful antioxidant which has shown the ability to lower serum cholesterol levels and cause regression of xanthomas in patients having homozygous familial hypercholesterolemia (A. Yamamoto, et al., Am. J. Cardiol., 57, 29H-35H (1986)). However, treatment with
10 probucol alone sometimes shows erratic control of LDL and frequent lowering of HDL (The Pharmacological Basis of Therapeutics, p. 891). Probucol is contraindicated for patients with progressive myocardial damage and/or
15 ventricular arrhythmias.

A class of materials which operates by another mechanism to lower LDL cholesterol comprises bile acid sequestering agents. Such agents are typically anion exchange polymers administered orally to a patient. As
20 the agent passes through the gut, anions of bile acids are sequestered by the agent and excreted. Such sequestering has been speculated to prevent reabsorption by the gut, for example the ileum, thereby preventing conversion of the bile acids into cholesterol. One such bile acid
25 sequestering agent is cholestyramine, a styrene-divinylbenzene copolymer containing quaternary ammonium cationic groups capable of binding bile acids. It is believed that cholestyramine binds the bile acids in the intestinal tract, thereby interfering with their normal
30 enterohepatic circulation. This effect is described by Reihner et al., in "Regulation of hepatic cholesterol metabolism in humans: stimulatory effects of cholestyramine on HMG-CoA reductase activity and low density lipoprotein receptor expression in gallstone

13

patients", Journal of Lipid Research, 31, 2219-2226 (1990). Further description of this effect is found in Suckling et al. in "Cholesterol Lowering and bile acid excretion in the hamster with cholestyramine treatment", Atherosclerosis, 89, 183-90 (1991). This results in an increase in liver bile acid synthesis because of the liver using cholesterol as well as an upregulation of the liver LDL receptors which enhances clearance of cholesterol and decreases serum LDL cholesterol levels.

10 Another bile acid sequestering agent is colestipol, a copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane. Colestipol is described in U.S. Patent No. 3,692,895. A frequent side effect of colestipol and of cholestyramine is gastric distress.

15 Additional bile acid sequestering agents are described in U.S. Patent No. 5,703,188, assigned to Geltex Pharmaceuticals Inc. For example, one such bile acid sequestering agent is 3-methacrylamidopropyltrimethylammonium chloride
20 copolymerized with ethylene glycol dimethacrylate to yield a copolymer.

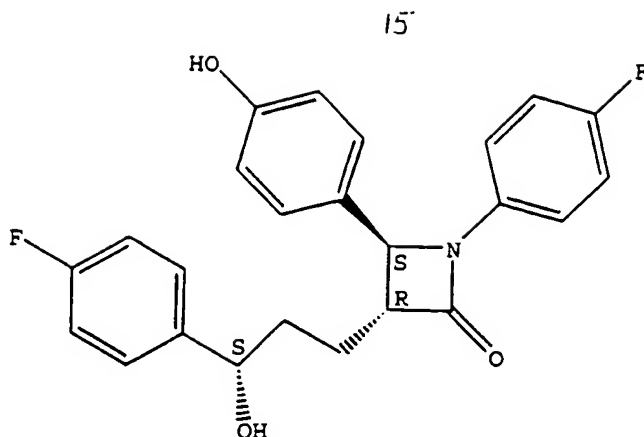
Yet another class materials proposed as bile acid sequestering agents comprises particles comprising amphiphilic copolymers having a crosslinked shell domain
25 and an interior core domain (Patent application no. PCT/US 97/11610). Structures and preparation of such crosslinked amphiphilic copolymers are described in PCT/US97/11345. Such particles have been given the common name of "knedels" (K.B. Thurmond et al., J. Am. Chem. Soc., 118
30 (30), 7239-40 (1996)).

Nicotinic acid (niacin) is a B-complex vitamin reported as early as 1955 to act as a hypolipidemic agent (R. Altschl, et al., Arch. Biochem. Biophys., 54, 558-9 (1955)). It is sometimes used to raise low HDL levels and

lower VLDL and LDL levels. ¹⁴ Useful commercial formulations of nicotinic acid include Niacor, Niaspan, Nicobid, Nicolar, Slo-Niacin. Nicotinic acid is contraindicated for patients having hepatic dysfunction, active peptic ulcer, or arterial bleeding. Another compound in this class useful for cardiovascular indications is niceritrol (T. Kazumi et al., Curr. Ther. Res., 55, 546-51). J. Sasaki et al. (Int. J. Clin. Pharm. Ther., 33 (7), 420-26 (1995)) describes a reduction in cholesterol ester transfer activity by niceritrol monotherapy. Acipimox (5-methyl pyrazine-2-carboxylic acid 4-oxide, U.S. Patent No. 4,002,750) is structurally similar to nicotinic acid and has antihyperlipidemic activity.

A study by Wetterau et al. (Science, 282, 751-54 (1998)) describes a number of alkylpiperidine compounds, isoindole compounds, and fluorene compounds useful for inhibiting microsomal triglyceride transfer protein (MTP inhibitors). Rodents and Watanabe-heritable hyperlipidemic rabbits treated with these compounds show decreased production of lipoprotein particles.

Cholesterol absorption antagonists may also be useful for the treatment of prophylaxis of cardiovascular diseases such as hypercholesterolemia or atherosclerosis. For example, azetidinones such as SCH 58235 ([3R-[3 α (S*), 4 β]]-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone) (formula A-1), described in J. Med. Chem., 41(6), 973-980 (1998), are useful cholesterol absorption antagonists. SCH 58235 is further described by Van Heek et al. in J. Pharmacol. Exp. Ther., 283(1), 157-163 (1997). Further azetidinone compounds useful for treatment or prophylaxis of cardiovascular disease are described in U.S. Patent No. 5,767,115.



A-1

[3R-[3a(S*),4b]]-1-(4-fluorophenyl)-3-
[3-(4-fluorophenyl)-3-hydroxypropyl]-4-
(4-hydroxyphenyl)-2-azetidinone

Phytosterols, and especially stanols have been shown
5 to effectively inhibit cholesterol absorption from the
gastrointestinal tract, and to negatively affect
cholesterol synthesis. Phytosterols are expected to slow
or inhibit the progress and formation of certain
cardiovascular conditions, including hyperlipidemic
10 conditions such as hypercholesterolemia and
atherosclerosis. Stanols are 5 α saturated derivatives of
phytosterols. (Straub, U.S. Patent No. 5,244,887). It
has been suggested that phytosterols lower blood
cholesterol levels by reducing the absorption of
15 cholesterol from the intestine (Ling and Jones,
"Minireview Dietary Phytosterols: A Review of Metabolism,
Benefits and Side Effects," Life Sciences, 57 (3), 195-206
(1995)).

Sitostanol, clionastanol, 22,23-dihydrobrassica-
20 stanol, campestanol, and mixtures thereof contained in
food additives intended to reduce cholesterol absorption
from foods and beverages containing cholesterol are
described by Straub in U.S. Patent Number 5,244,887.

A beta-sitostanol fatty¹⁶ acid ester or fatty acid ester mixture which lowers cholesterol in serum is described by Miettinen et al. in U.S. Patent Number 5,502,045.

5 A stanol composition containing in sitostanol and campestanol which effectively lowers serum cholesterol levels when incorporated into edibles is described by Wester et al. in WO 9806405.

A therapeutic composition of one or more oxysterols
10 and a suitable carrier to inhibit cholesterol absorption from the diet is described by Haines in U.S. Patent Number 5,929,062.

Cardiovascular disease is also caused or aggravated by hypertension. Hypertension is defined as persistently
15 high blood pressure. Generally, adults are classified as being hypertensive when systolic blood pressure is persistently above 140 mmHg or when diastolic blood pressure is above 90 mmHg. Long-term risks for cardiovascular mortality increase in a direct relationship
20 with persistent blood pressure (E. Braunwald, Heart Disease, 5th ed., W.B. Saunders & Co., Philadelphia, 1997, pp. 807-823). Various mechanisms have been advantageously exploited to control hypertension. For example, useful antihypertensive agents can include, without limitation,
25 an andrenergic blocker, a mixed alpha/beta andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker, an andrenergic stimulant, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, a
30 diuretic, or a vasodilator. A particularly useful antihypertensive agent is eplerenone (see, for example, U.S. Patent No. 4,559,332). Eplerenone lowers blood pressure by functioning as a diuretic. Eplerenone was formerly called epoxymexrenone.

Some combination therapies for the treatment of cardiovascular disease have been described in the literature. Combinations of IBAT inhibitors with HMG CoA reductase inhibitors useful for the treatment of
5 cardiovascular disease are disclosed in U.S. Patent Application No. 09/037,308 and in PCT Patent Application No. 98/40375.

A combination therapy of fluvastatin and niceritrol is described by J. Sasaki et al. (Id.). Those researchers
10 conclude that the combination of fluvastatin with niceritrol "at a dose of 750 mg/day dose does not appear to augment or attenuate beneficial effects of fluvastatin."

L. Cashin-Hemphill et al. (J. Am. Med. Assoc., 264
15 (23), 3013-17 (1990)) describe beneficial effects of a combination therapy of colestipol and niacin on coronary atherosclerosis. The described effects include nonprogression and regression in native coronary artery lesions.

20 A combination therapy of acipimox and simvastatin shows beneficial HDL effects in patients having high triglyceride levels (N. Hoogerbrugge et al., J. Internal Med., 241, 151-55 (1997)).

Sitostanol ester margarine and pravastatin
25 combination therapy is described by H. Gylling et al. (J. Lipid Res., 37, 1776-85 (1996)). That therapy is reported to simultaneously inhibit cholesterol absorption and lower LDL cholesterol significantly in non-insulin-dependent diabetic men.

30 Brown et al. (New Eng. J. Med., 323 (19), 1289-1339 (1990)) describe a combination therapy of lovastatin and colestipol which reduces atherosclerotic lesion progression and increase lesion regression relative to lovastatin alone.

Scott (PCT Patent Application No. WO 99/11260) describes combinations of atorvastatin (an HMG CoA reductase inhibitor) with an antihypertensive agent for the treatment of angina pectoris, atherosclerosis, 5 combined hypertension and hyperlipidemia, and symptoms of cardiac risk.

Egan et al. (PCT Patent Application No. WO 96/40255) describe a combination therapy of an angiotension II antagonist and an epoxy-steroidal aldosterone antagonist. 10 The epoxy-steroidal aldosterone antagonist in the Egan application includes eplerenone.

The above references show continuing need to find safe, effective agents for the prophylaxis or treatment of cardiovascular diseases.

15

Summary of the Invention

To address the continuing need to find safe and effective agents for the prophylaxis and treatment of cardiovascular diseases, combination therapies of 20 cardiovascular drugs are now reported.

Among its several embodiments, the present invention provides a combination therapy comprising the use of a first amount of an IBAT inhibitor and a second amount of another cardiovascular therapeutic useful in the 25 prophylaxis or treatment of hyperlipidemia or atherosclerosis, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds. For example one of the 30 many embodiments of the present invention is a therapeutic composition comprising first amount of an IBAT inhibitor and a second amount of a microsomal triglyceride transfer protein inhibitor (MTP inhibitor), wherein the first and second amounts together comprise an anti-hyperlipidemic

condition effective amount or ¹⁹an anti-atherosclerotic condition effective amount of the compounds. The IBAT inhibitor in the embodiments of this invention is preferably a benzothiepine IBAT inhibitor. In another
5 embodiment, the IBAT inhibitor can be a benzothiazepine IBAT inhibitor. In still another embodiment, the IBAT inhibitor can be a naphthalene IBAT inhibitor.

The present invention further provides a therapeutic composition comprising a first amount of an IBAT inhibitor
10 and a second amount of a cholesterol absorption antagonist, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds.

15 The present invention further provides a therapeutic combination comprising a first amount of an ileal bile acid transport inhibiting compound and a second amount of an antihypertensive compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic
20 condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds.

In another embodiment, the present invention also
25 includes a therapeutic combination comprising a first amount of an ileal bile acid transport inhibiting compound and a second amount of an antiobesity compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-
30 atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds. For example, the antiobesity compound can comprise orlistat. Orlistat is described in European Patent No. EP 0 129 748.

Among its several embodiments, the present invention further provides a combination comprising a first amount of an IBAT inhibitor and a second amount of another cardiovascular therapeutic useful in the prophylaxis or treatment of hyperlipidemia or atherosclerosis, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds. For example one of the many embodiments of the present invention is a combination comprising therapeutic dosages of an IBAT inhibitor and a phytosterol. A preferred embodiment of the present invention is a combination comprising therapeutic dosages of a benzothiepine IBAT inhibitor and a phytosterol. In another preferred embodiment, the present invention embraces a combination comprising an IBAT inhibitor and a stanol.

A still further embodiment of the instant invention comprises the use of any of the cardiovascular combination therapies described herein for the prophylaxis or treatment of hypercholesterolemia or atherosclerosis.

In another embodiment the present invention provides a method for the prophylaxis or treatment of a hyperlipidemic condition or disorder in a mammal which comprises administering a first amount of an ileal bile acid transport inhibitor compound and a second amount of a microsomal triglyceride transfer protein inhibiting compound wherein the first amount and the second amount together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds.

In another embodiment the present invention provides a method for the prophylaxis or treatment of a hyperlipidemic condition or disorder in a mammal which

comprises administering a first amount of an ileal bile
acid transport inhibitor compound and a second amount of a
cholesterol absorption antagonist compound wherein the
first amount and the second amount together comprise an
5 anti-hyperlipidemic condition effective amount, an anti-
atherosclerotic condition effective amount, or an anti-
hypercholesterolemic condition effective amount of the
compounds.

In another embodiment the present invention provides
10 a method for the prophylaxis or treatment of a
hyperlipidemic condition or disorder in a mammal which
comprises administering a therapeutic combination
comprising a first amount of an ileal bile acid transport
inhibiting compound and a second amount of an
15 antihypertensive compound wherein the first amount and the
second amount together comprise an anti-hyperlipidemic
condition effective amount of the compounds.

In another embodiment the present invention provides
a method for the prophylaxis or treatment of a
20 hyperlipidemic condition or disorder in a mammal which
comprises administering a first amount of an ileal bile
acid transport inhibitor compound and a second amount of a
phytosterol compound wherein the first amount and the
second amount together comprise an anti-hyperlipidemic
25 condition effective amount, an anti-atherosclerotic
condition effective amount, or an anti-
hypercholesterolemic condition effective amount of the
compounds. Preferably the phytosterol compound comprises
a stanol.

30 In another embodiment the present invention provides
a kit for achieving a therapeutic effect in a mammal
comprising an amount of an ileal bile acid transport
inhibiting compound in a first unit dosage form; an amount
of a microsomal triglyceride transfer protein inhibiting

22

compound in a second unit dosage form; and container means for containing said first and second unit dosage forms.

In another embodiment the present invention provides a kit for achieving a therapeutic effect in a mammal comprising an amount of an ileal bile acid transport inhibiting compound in a first unit dosage form; an amount of a cholesterol absorption antagonist compound in a second unit dosage form; and container means for containing said first and second unit dosage forms.

10 In another embodiment the present invention provides a kit for achieving a therapeutic effect in a mammal comprising an amount of an ileal bile acid transport inhibiting compound in a first unit dosage form; an amount of an antihypertensive compound in a second unit dosage form; and container means for containing said first and second unit dosage forms.

In another embodiment the present invention provides a kit for achieving a therapeutic effect in a mammal comprising an amount of an ileal bile acid transport inhibiting compound in a first unit dosage form; an amount of a phytosterol compound in a second unit dosage form; and container means for containing said first and second unit dosage forms. Preferably the phytosterol compound comprises a stanol.

25 Further scope of the applicability of the present invention will become apparent from the detailed description provided below. However, it should be understood that the following detailed description and examples, while indicating preferred embodiments of the invention, are given by way of illustration only since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

²³
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following detailed description is provided to aid those skilled in the art in practicing the present invention. Even so, this detailed description should not be construed to unduly limit the present invention as modifications and variations in the embodiments discussed herein can be made by those of ordinary skill in the art without departing from the spirit or scope of the present inventive discovery.

The contents of each of the references cited herein, including the contents of the references cited within these primary references, are herein incorporated by reference in their entirety.

a. Definitions

The following definitions are provided in order to aid the reader in understanding the detailed description of the present invention:

"Benzothiepine IBAT inhibitor" means an ileal bile acid transport inhibitor which comprises a therapeutic compound comprising a 2,3,4,5-tetrahydro-1-benzothiepine 1,1-dioxide structure or a 2,3,4,5-tetrahydro-1-benzothiepine 1-oxide structure.

"Benzothiazepine IBAT inhibitor" means an ileal bile acid transport inhibitor which comprises a therapeutic compound comprising a 2,3,4,5-tetrahydro-1-benzothi-4-azepine 1,1-dioxide structure or a 2,3,4,5-tetrahydro-1-benzothi-5-azepine 1,1-dioxide structure.

"Naphthalene IBAT inhibitor" means an ileal bile acid transport inhibitor which comprises a therapeutic compound comprising a substituted naphthalene structure.

"Nicotinic acid derivative" means a therapeutic compound comprising a pyridine-3-carboxylate structure or

24
a pyrazine-2-carboxylate structure, including acid forms, salts, esters, zwitterions, and tautomers. Nicotinic acid derivatives include, for example, nicotinic acid (niacin), niceritrol, and acipimox.

5 A "phytosterol" means any steroid naturally or synthetically derived having about C₈ to about C₁₀ carbon aliphatic side chains at position 17, and at least one alcoholic hydroxyl group (Miller-Keane, Encyclopedia & Dictionary of Medicine, Nursing, & Allied Health, 5th
10 ed.). As used herein, the term "phytosterol" includes stanols.

"Stanol" means a class of phytosterols having a 5 α -saturation.

"Combination therapy" means the administration of two
15 or more therapeutic agents to treat a hypertensive condition or a hyperlipidemic condition, for example atherosclerosis and hypercholesterolemia. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner,
20 such as in a single dosage form having a fixed ratio of active ingredients or in multiple, separate dosage forms for each inhibitor agent. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case,
25 the treatment regimen will provide beneficial effects of the drug combination in treating the hypertensive condition or the hyperlipidemic condition.

The phrase "therapeutically effective" is intended to qualify the combined amount of inhibitors in the
30 combination therapy. This combined amount will achieve the goal of reducing or eliminating the hypertensive condition or the hyperlipidemic condition.

"Therapeutic compound" means a compound useful in the prophylaxis or treatment of a hypertensive condition or a

25

hyperlipidemic condition, including atherosclerosis and hypercholesterolemia.

5 b. Combinations

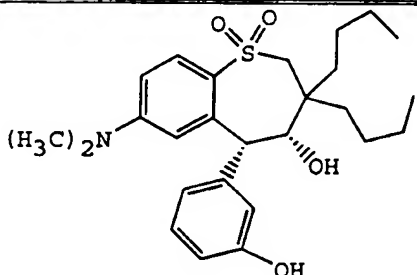
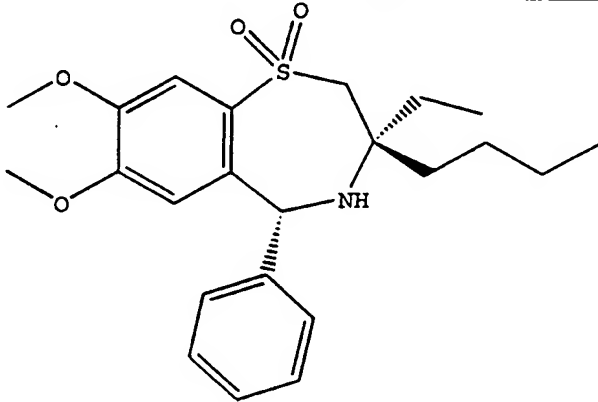
The combinations of the present invention will have a number of uses. For example, through dosage adjustment and medical monitoring, the individual dosages of the
10 therapeutic compounds used in the combinations of the present invention will be lower than are typical for dosages of the therapeutic compounds when used in monotherapy. The dosage lowering will provide advantages including reduction of side effects of the individual
15 therapeutic compounds when compared to the monotherapy. In addition, fewer side effects of the combination therapy compared with the monotherapies will lead to greater patient compliance with therapy regimens.

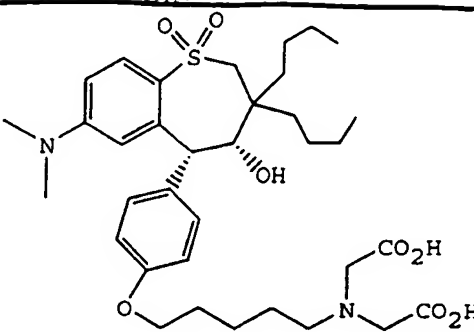
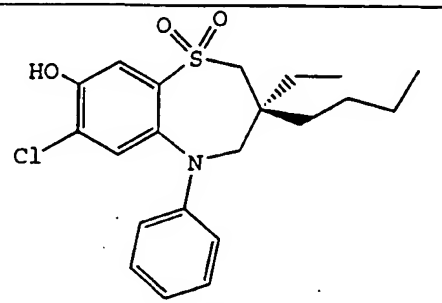
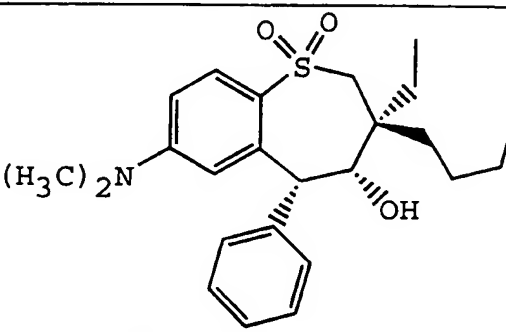
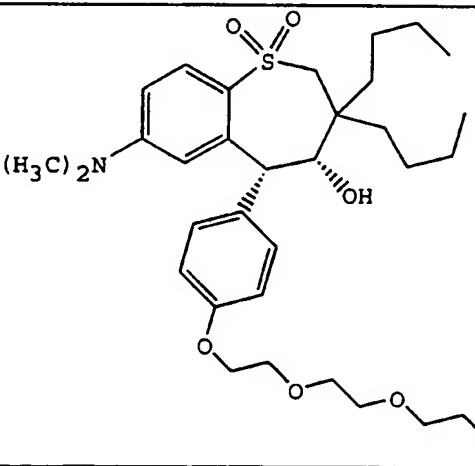
Another use of the present invention will be in
20 combinations having complementary effects or complementary modes of action. For example, IBAT inhibitors frequently lower LDL lipoprotein but also lower HDL lipoprotein. In contrast, CETP inhibitors raise HDL. A therapeutic combination of an IBAT inhibitor and a CETP inhibitor
25 will, when dosages are optimally adjusted, lower LDL yet maintain or raise HDL.

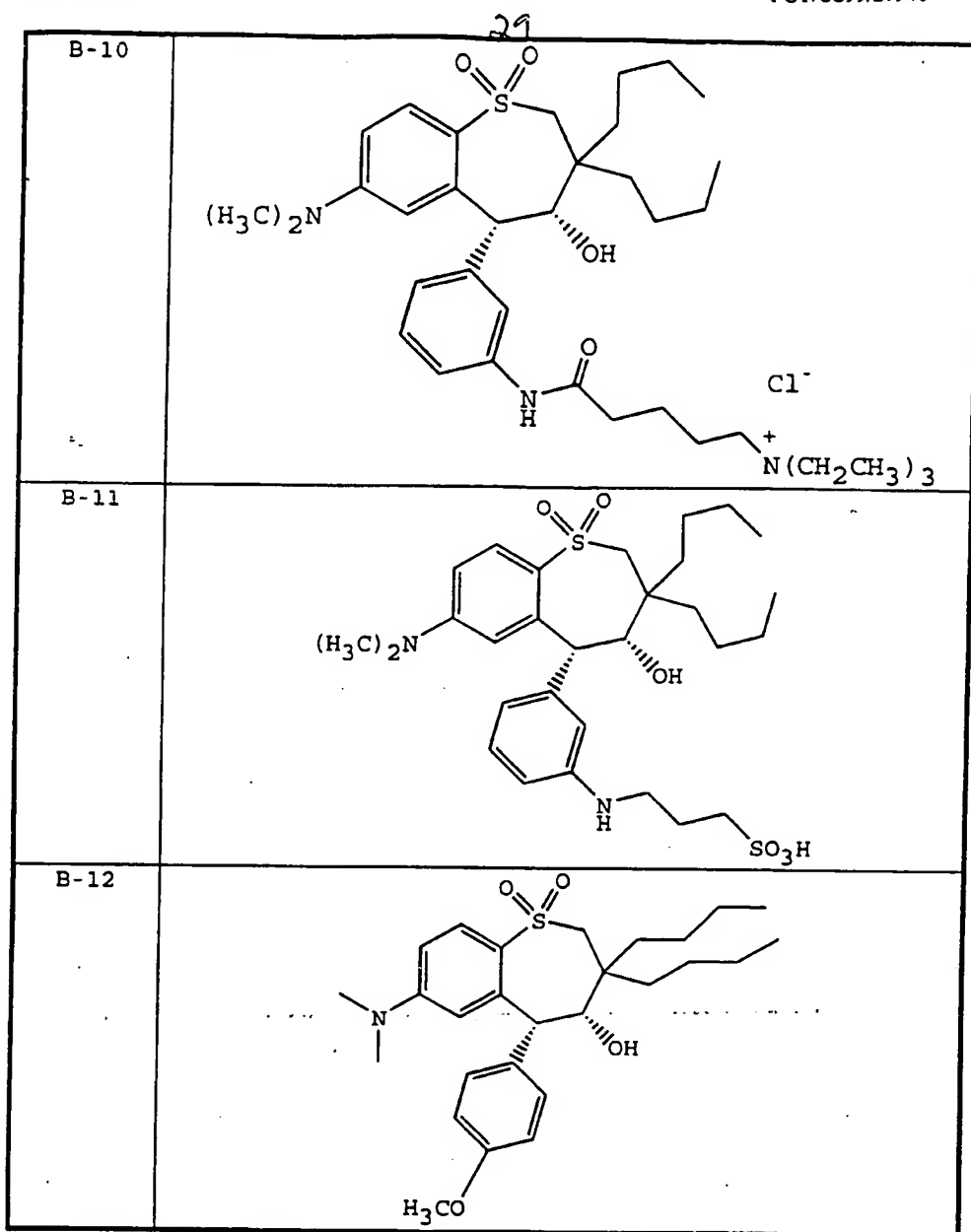
Compounds useful in the present invention encompass a wide range of therapeutic compounds. IBAT inhibitors useful in the present invention are disclosed in patent
30 application no. PCT/US95/10863, herein incorporated by reference. More IBAT inhibitors are described in PCT/US97/04076, herein incorporated by reference. Still further IBAT inhibitors useful in the present invention are described in U.S. Application Serial No. 08/816,065,

herein incorporated by reference. ²⁶ More IBAT inhibitor compounds useful in the present invention are described in WO 98/40375, herein incorporated by reference. Additional IBAT inhibitor compounds useful in the present invention are described in U.S. Application Serial No. 08/816,065, herein incorporated by reference. IBAT inhibitors of particular interest in the present invention are shown in Table 1, as well as the diastereomers, enantiomers, racemates, salts, and tautomers of the IBAT inhibitors of Table 1.

Table 1.

Compound Number	Structure
B-1	
B-2	 <p>(3R,5R)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1,4-benzothiazepine 1,1-dioxide</p>

B-6	<p style="text-align: center;">26</p> 
B-7	
B-8	
B-9	 <p style="text-align: right;">Cl⁻</p> <p style="text-align: right;">N(CH₂CH₃)₃⁺</p>



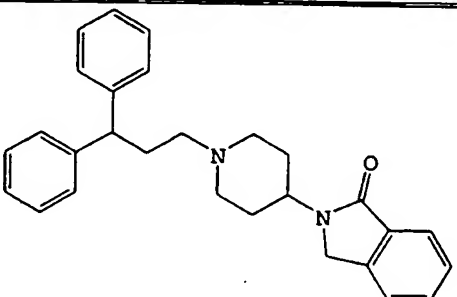
U.S. patents referenced in Table 4 are each herein⁴⁵
incorporated by reference.

Table 4.

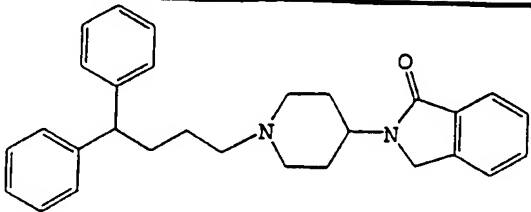
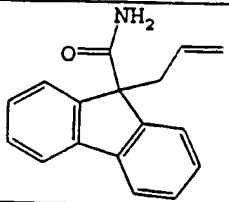
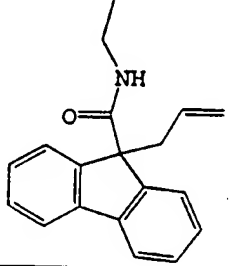
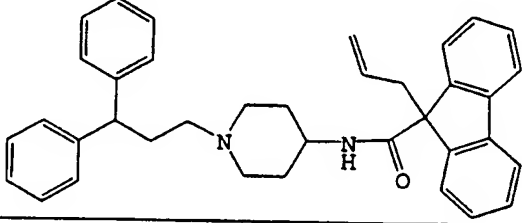
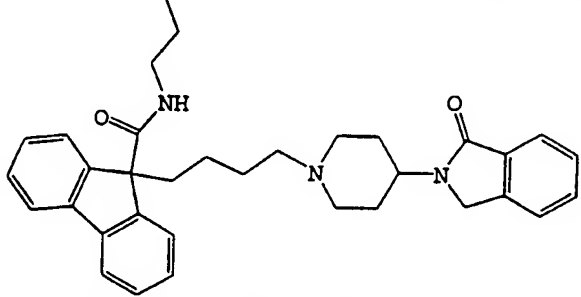
Compound Number	Common Name	CAS Registry Number	U.S. Patent Reference for Compound Per Se
G-41	Clofibrate	637-07-0	3,262,850
G-70	Fenofibrate	49562-28-9	4,058,552
G-38	Ciprofibrate	52214-84-3	3,948,973
G-20	Bezafibrate	41859-67-0	3,781,328
G-78	Gemfibrozil	25182-30-1	3,674,836

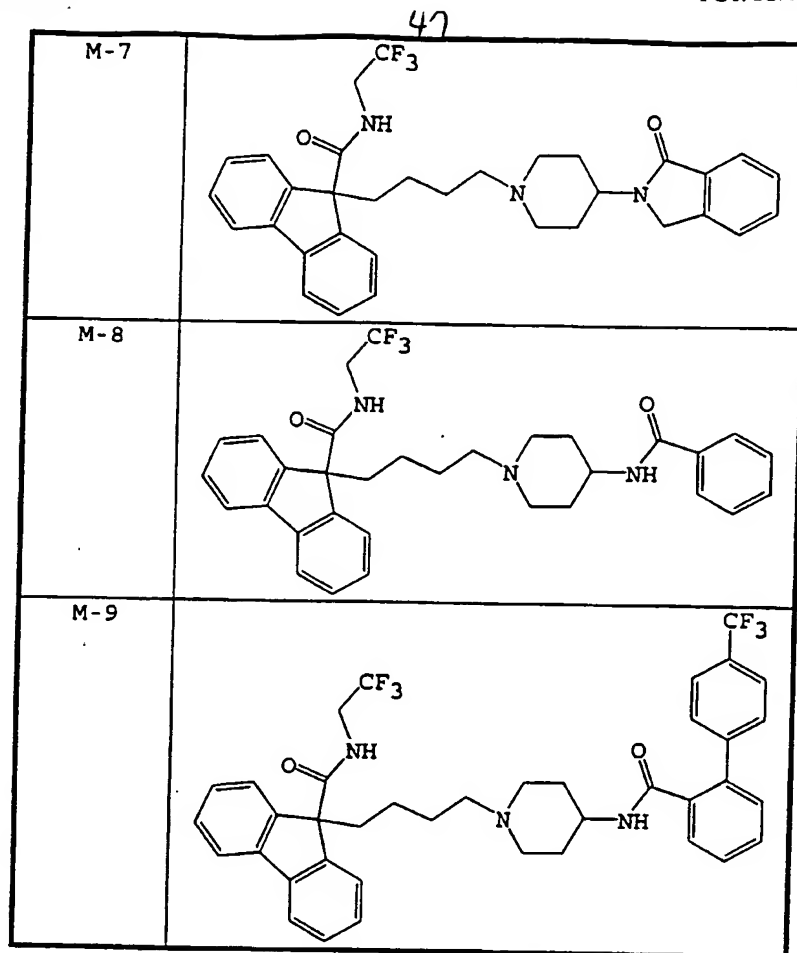
5 MTP inhibitor compounds useful in the combinations and methods of the present invention comprise a wide variety of structures and functionalities. Some of the MTP inhibitor compounds of particular interest for use in the present
10 invention are shown in Table 4b. The therapeutic compounds of Table 4b can be used in the present invention in a variety of forms, including acid form, salt form, racemates, enantiomers, zwitterions, and tautomers. Descriptions of the therapeutic compounds of Table 4b can be found in
15 Science, 282, 23 October 1998, pp. 751-754, herein incorporated by reference.

Table 4b.

Compound Number	Structure
M-1	

46

M-2	
M-3	
M-4	
M-5	
M-6	



Cholesterol absorption antagonist compounds useful in the combinations and methods of the present invention

5 comprise a wide variety of structures and functionalities. Some of the cholesterol absorption antagonist compounds of particular interest for use in the present invention are described in U.S. Patent No. 5,767,115, herein incorporated by reference. Further cholesterol absorption

10 antagonist compounds of particular interest for use in the present invention, and methods for making such cholesterol absorption antagonist compounds are described in U.S. Patent No. 5,631,365, herein incorporated by reference. A

particularly preferred cholesterol absorption antagonist
for use in the combinations and methods of the present
invention is SCH 58235 ([3R-[3 α (S*),4 β)]-1-(4-
fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-
5 hydroxyphenyl)-2-azetidinone).

In another embodiment the present invention includes
a therapeutic combination comprising a first amount of an
ileal bile acid transport inhibiting compound and a second
amount of a phytosterol compound wherein the first amount
10 and the second amount together comprise an anti-
hyperlipidemic condition effective amount, an anti-
atherosclerotic condition effective amount, or an anti-
hypercholesterolemic condition effective amount of the
compounds. A number of phytosterols are described by Ling
15 and Jones in "Dietary Phytosterols: A Review of
Metabolism, Benefits and Side Effects," Life Sciences, 57
(3), 195-206 (1995). Without limitation, some
phytosterols of particular use in the the combination of
the present invention are shown in Table 4c. Phytosterols
20 are also referred to generally by Nes (Physiology and
Biochemistry of Sterols, American Oil Chemists' Society,
Champaign, Ill., 1991, Table 7-2). Especially preferred
among the phytosterols for use in the combination of the
present invention are saturated phytosterols or stanols.
25 Additional stanols are also described by Nes (Id.) and are
useful in the combination of the present invention. In
the combination of the present invention, the phytosterol
preferably comprises a stanol. In one preferred
embodiment the stanol is campestanol. In another preferred
30 embodiment the stanol is cholestanol. In another preferred
embodiment the stanol is clionastanol. In another
preferred embodiment the stanol is coprostanol. In another
preferred embodiment the stanol is 22,23-
dihydrobrassicastanol. In another preferred embodiment the

49

stanol is epicholesterol. In another preferred embodiment
the stanol is fucostanol. In another preferred embodiment
the stanol is stigmastanol. In the combination of the
present invention, the IBAT inhibitor is preferably a
5 benzothiazepine IBAT inhibitor. In one preferred
embodiment, the benzothiazepine IBAT inhibitor is compound
B-2. In another preferred embodiment, the benzothiazepine
IBAT inhibitor is compound B-7. In yet another preferred
embodiment, the IBAT inhibitor is a benzothiepine IBAT
10 inhibitor. Each of the following benzothiepine IBAT
inhibitors represents a separate preferred embodiment of
the present invention.

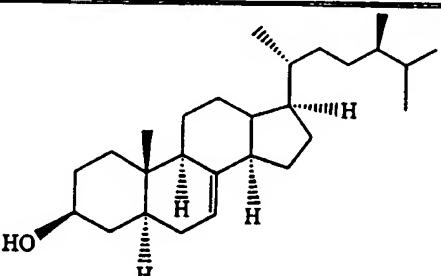
- B-1.
- B-3.
- 15 B-4.
- B-5.
- B-6.
- B-8.
- B-9.
- 20 B-10.
- B-11.
- B-12.
- B-13.
- B-14.
- 25 B-15.
- B-16.
- B-17.
- B-18.
- B-19.
- 30 B-21.
- B-22.
- B-23.
- B-24.
- B-25.

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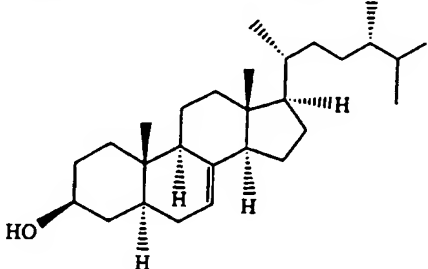
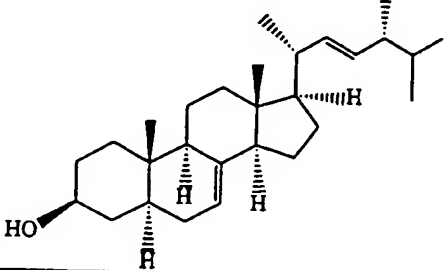
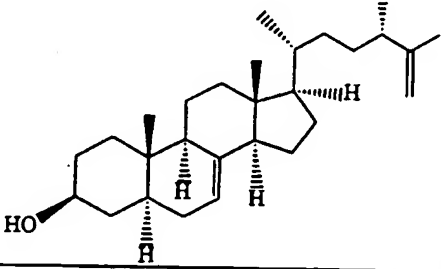
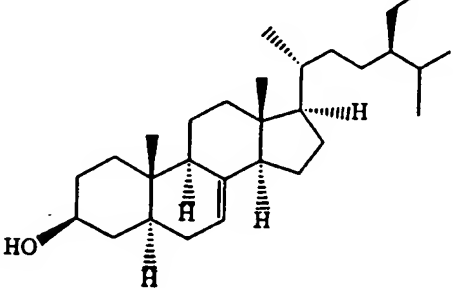
- B-26.
B-27.
B-28.
B-29.
5 B-30.
B-31.
B-32.
B-33.
B-34.
10 B-35.
B-36.
B-37.
B-38.
B-39.
- 15 In yet another preferred embodiment, the IBAT inhibitor is a naphthalene IBAT inhibitor, for example, compound B-20.

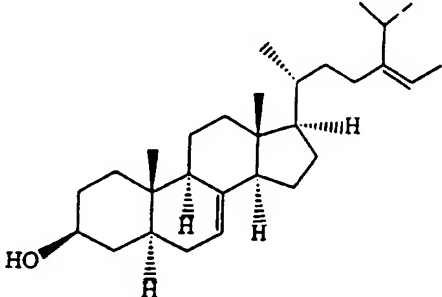
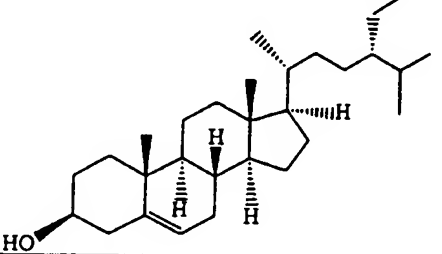
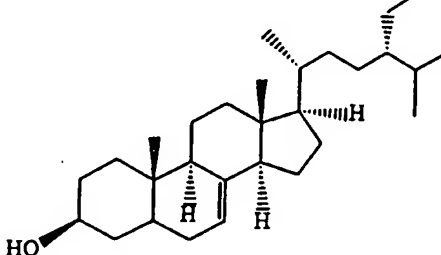
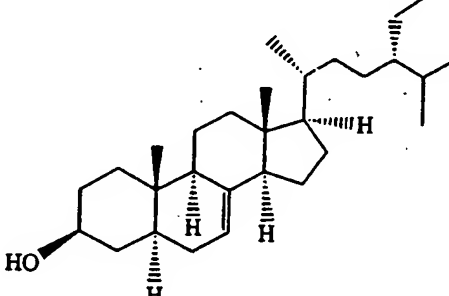
Table 4c.

20

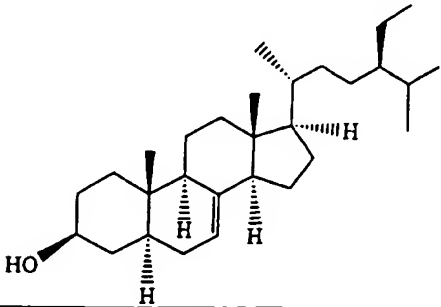
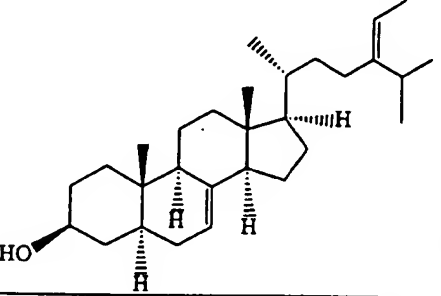
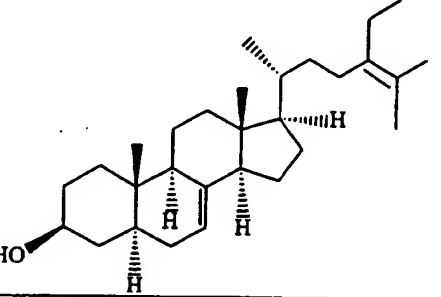
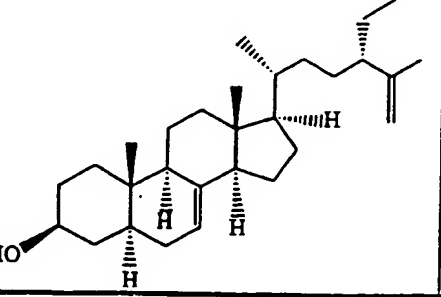
Compound No.	Compound Structure	Compound Name
P-1	 <chem>CC(C)[C@H](CCCC(C)C)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C</chem>	Campesterol

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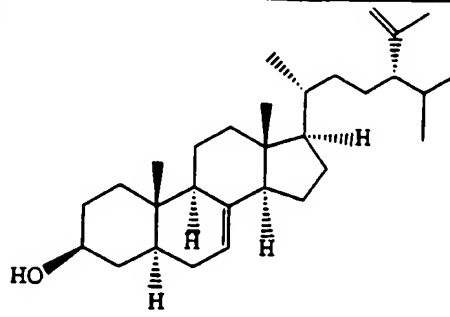
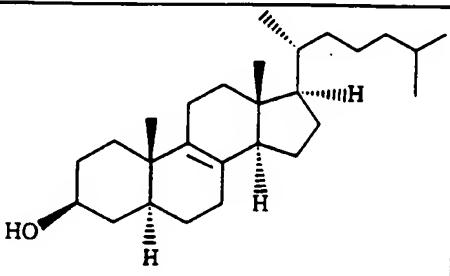
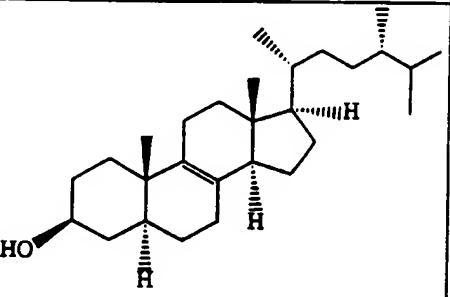
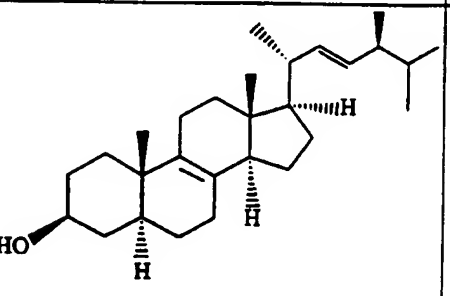
P-2		22-Dihydrobrassicasterol
P-3		Brassicasterol
P-4		Codisterol
P-5		β -sitosterol

P-6	 <p>The chemical structure of α-sitosterol is shown. It is a steroid with a hydroxyl group at C-3 (wedged), a double bond at C-5, and methyl groups at C-10 and C-13 (wedged). The side chain at C-17 consists of a propyl group (wedged), a methylene group (dashed), and an isopentenyl group (wedged).</p>	α -sitosterol
P-7	 <p>The chemical structure of γ-sitosterol is shown. It is a steroid with a hydroxyl group at C-3 (wedged), a double bond at C-5, and methyl groups at C-10 and C-13 (wedged). The side chain at C-17 consists of a propyl group (wedged), a methylene group (wedged), and an isopentenyl group (wedged).</p>	γ -sitosterol
P-8	 <p>The chemical structure of Clionasterol is shown. It is a steroid with a hydroxyl group at C-3 (wedged), a double bond at C-5, and methyl groups at C-10 and C-13 (wedged). The side chain at C-17 consists of a propyl group (wedged), a methylene group (wedged), and an isopentenyl group (wedged).</p>	Clionasterol
P-9	 <p>The chemical structure of Poriferasterol is shown. It is a steroid with a hydroxyl group at C-3 (wedged), a double bond at C-5, and methyl groups at C-10 and C-13 (wedged). The side chain at C-17 consists of a propyl group (wedged), a methylene group (wedged), and an isopentenyl group (wedged).</p>	Poriferasterol

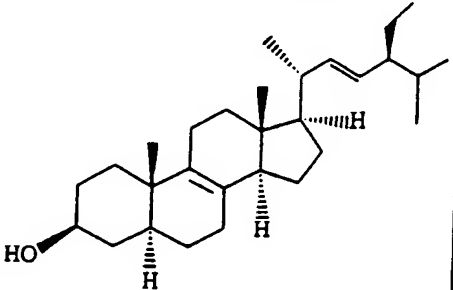
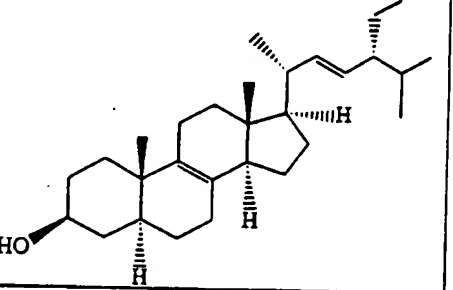
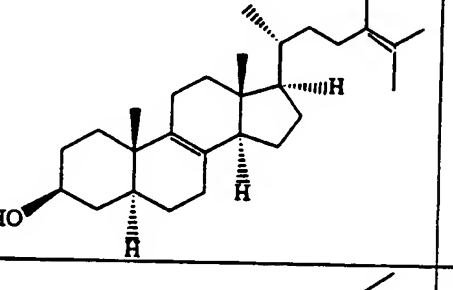
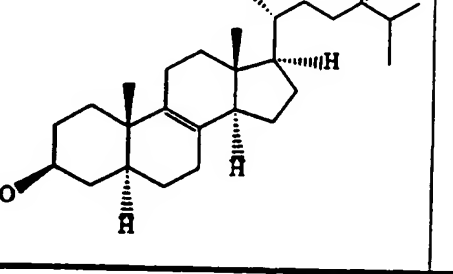
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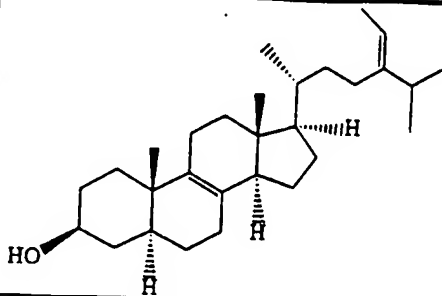
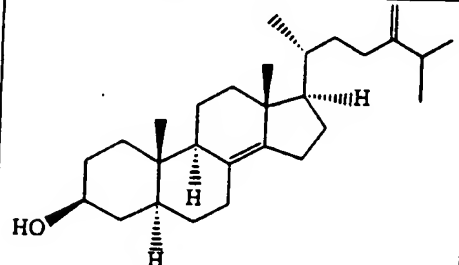
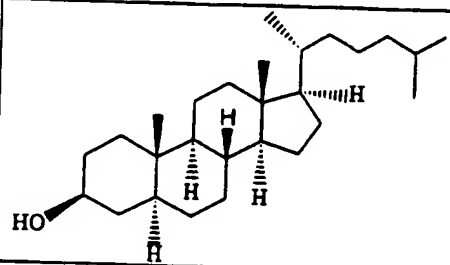
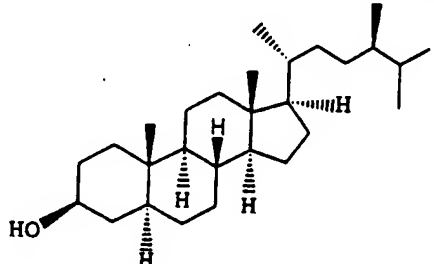
P-10		Stigmasterol
P-11		Isofucosterol
P-12		Fucosterol
P-13		Clerosterol

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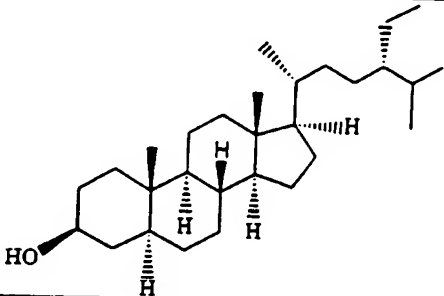
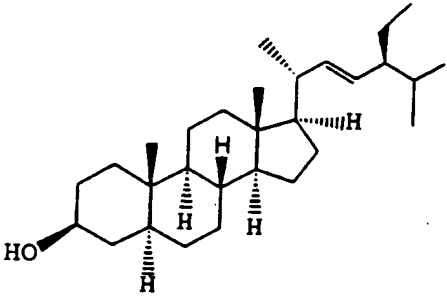
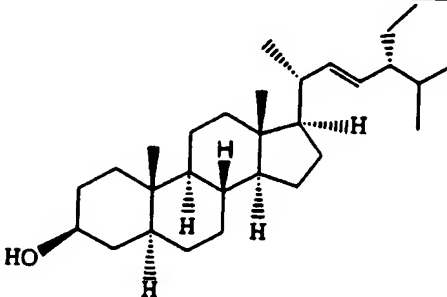
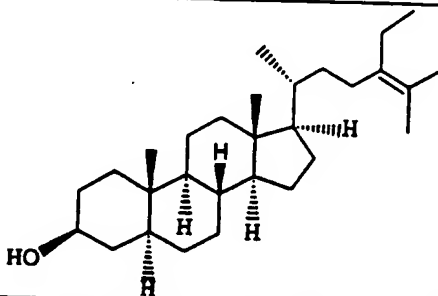
P-14		Nervisterol
P-15		Lathosterol
P-16		Fungisterol
P-17		Stellasterol

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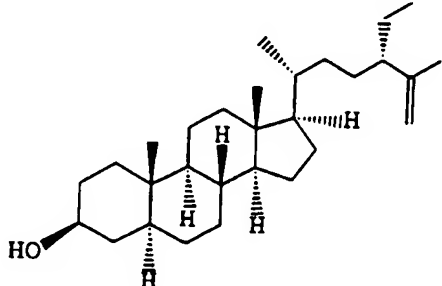
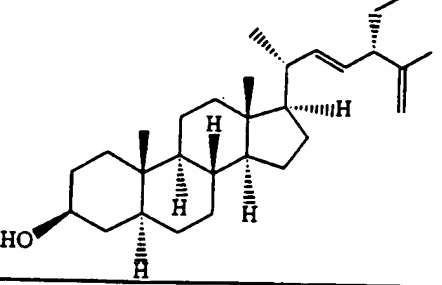
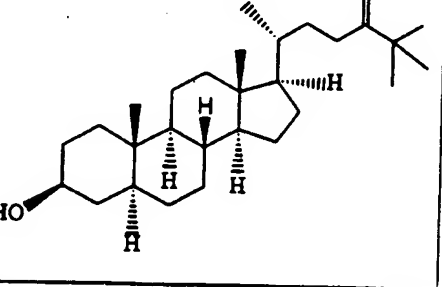
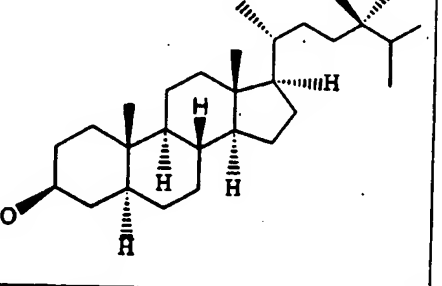
P-18		Spinasterol
P-19		Chondrillasterol
P-20		Peposterol
P-21		Avenasterol

P-22	 <p>Chemical structure of Isoavenasterol, a sterol with a hydroxyl group at C-3, a double bond at C-5, and a branched side chain at C-17.</p>	Isoavenasterol
P-23	 <p>Chemical structure of Fecosterol, a sterol with a hydroxyl group at C-3, a double bond at C-5, and a branched side chain at C-17.</p>	Fecosterol
P-24	 <p>Chemical structure of Cholestanol, a sterol with a hydroxyl group at C-3 and a branched side chain at C-17.</p>	Cholestanol
P-25	 <p>Chemical structure of Campestanol, a sterol with a hydroxyl group at C-3 and a branched side chain at C-17.</p>	Campestanol

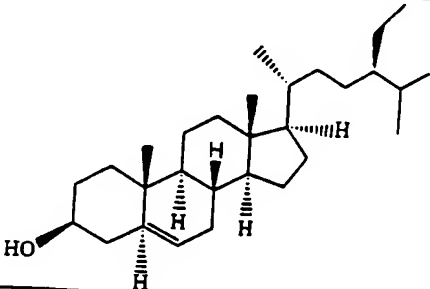
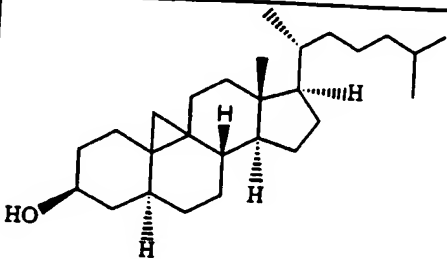
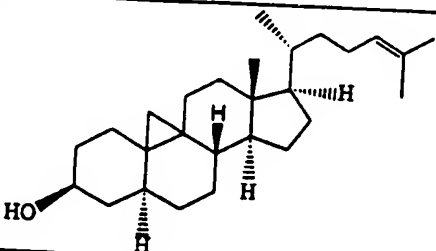
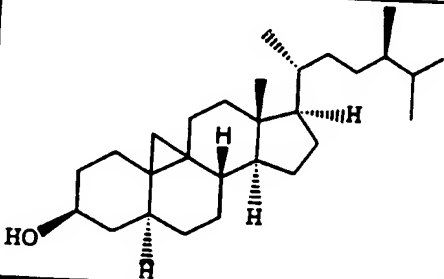
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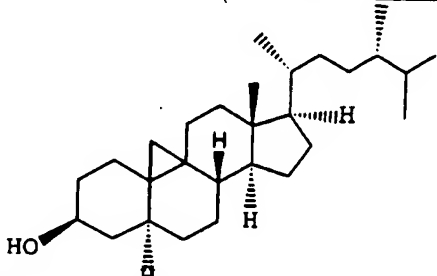
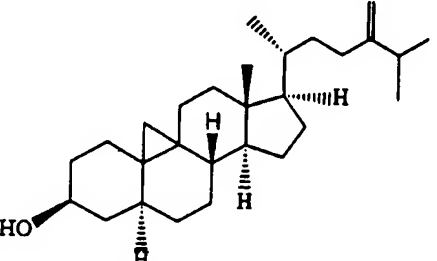
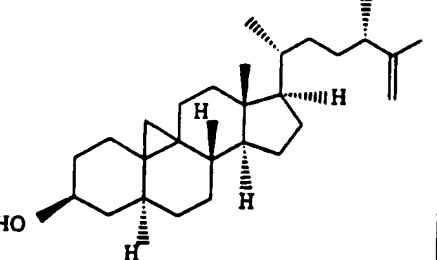
P-26		24β- Ethylcholestanol
P-27		24α-Ethyl-22- dehydrochole- stanol
P-28		24β-Ethyl-22- dehydrochole- stanol
P-29		24-Ethyl-24(25)- dehydrochole- stanol

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P-30		24β-Ethyl-25-dehydrocholestanol
P-31		24β-Ethyl-22,25-bisdehydrocholestanol
P-32		24-Methylene-25-methylcholestanol
P-33		24,24-Dimethylcholestanol

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P-34		24α- Ethylcholestan-3α- ol
P-35		Pollinastanol
P-36		24-Dehydropollina- stanol
P-37		24-α- Methylpollina- stanol

P-38		24- β -Methylpollinastanol
P-39		24-Methylenepollinastanol
P-40		24 β -Methyl-25-dehydropollinastanol

In another embodiment the present invention encompasses a therapeutic combination of an IBAT inhibitor and an antihypertensive agent. Hypertension is defined as persistently high blood pressure. Generally, adults are classified as being hypertensive when systolic blood pressure is persistently above 140 mmHg or when diastolic blood pressure is above 90 mmHg. Long-term risks for cardiovascular mortality increase in a direct relationship with persistent blood pressure. (E. Braunwald, Heart Disease, 5th ed., W.B. Saunders & Co., Philadelphia, 1997, pp. 807-823.) Blood pressure is a function of cardiac

output and peripheral resistance of the vascular system and can be represented by the following equation:

$$BP = CO \times PR$$

5

wherein BP is blood pressure, CO is cardiac output, and PR is peripheral resistance. (*Id.*, p. 816.) Factors affecting peripheral resistance include obesity and/or functional constriction. Factors affecting cardiac output include venous constriction. Functional constriction of the blood vessels can be caused by a variety of factors including thickening of blood vessel walls resulting in diminishment of the inside diameter of the vessels. Another factor which affects systolic blood pressure is rigidity of the aorta (*Id.*, p. 811.)

Hypertension and atherosclerosis or other hyperlipidemic conditions often coexist in a patient. It is possible that certain hyperlipidemic conditions such as atherosclerosis can have a direct or indirect affect on hypertension. For example, atherosclerosis frequently results in diminishment of the inside diameter of blood vessels. Furthermore, atherosclerosis frequently results in increased rigidity of blood vessels, including the aorta. Both diminished inside diameter of blood vessels and rigidity of blood vessels are factors which contribute to hypertension.

Myocardial infarction is the necrosis of heart muscle cells resulting from oxygen deprivation and is usually caused by an obstruction of the supply of blood to the affected tissue. For example, hyperlipidemia or hypercholesterolemia can cause the formation of atherosclerotic plaques which can cause obstruction of blood flow and thereby cause myocardial infarction. (*Id.*, pp. 1185-1187.) Another major risk factor for myocardial

infarction is hypertension. ⁶²(Id., p. 815.) In other words, hypertension and hyperlipidemic conditions such as atherosclerosis or hypercholesterolemia work in concert to cause myocardial infarction.

5 Coronary heart disease is another disease which is caused or aggravated by multiple factors including hyperlipidemic conditions and hypertension. Control of both hyperlipidemic conditions and hypertension are important to control symptoms or disease progression of
10 coronary heart disease.

Angina pectoris is acute chest pain which is caused by decreased blood supply to the heart. Decreased blood supply to the heart is known as myocardial ischemia. Angina pectoris can be the result of, for example,
15 stenosis of the aorta, pulmonary stenosis, and ventricular hypertrophy. Some antihypertensive agents, for example amlodipine, control angina pectoris by reducing peripheral resistance.

It is now disclosed that a therapy which controls
20 hypertension and which in combination controls hyperlipidemic conditions will reduce risk from cardiovascular disease or symptoms of heart disease, for example coronary heart disease, myocardial infarction, or angina pectoris. Therefore one embodiment of the present
25 invention is directed to a therapeutic combination comprising a first amount of an ileal bile acid transport inhibiting compound and a second amount of an antihypertensive agent compound wherein the first amount and the second amount together comprise an anti-
30 hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds.

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Some antihypertensive agents useful in the present invention are shown in Table 5, without limitation. A wide variety of chemical structures are useful as antihypertensive agents in the combinations of the present invention and the agents can operate by a variety of mechanisms. For example, useful antihypertensive agents can include, without limitation, an andrenergic blocker, a mixed alpha/beta andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker, an andrenergic stimulant, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, a calcium channel blocker, a diuretic, or a vasodilator. Additional hypertensive agents useful in the present invention are described by R. Scott in U.S. Patent Application No. 60/057,276 (priority document for PCT Patent Application No. WO 99/11260), herein incorporated by reference.

Table 5.

Compound Number	Antihypertensive Classification	Compound Name	Dosage
N-1	andrenergic blocker	phenoxybenzamine	1-250 mg/day
N-2	andrenergic blocker	guanadrel	5-60 mg/day
N-3	andrenergic blocker	guanethidine	
N-4	andrenergic blocker	reserpine	
N-5	andrenergic blocker	terazosin	0.1-60 mg/day
N-6	andrenergic blocker	prazosin	0.5-75 mg/day
N-7	andrenergic blocker	polythiazide	0.25-10 mg/day
N-8	andrenergic stimulant	methyldopa	100-4000 mg/day
N-9	andrenergic stimulant	methyldopate	100-4000 mg/day

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N-10	adrenergic stimulant	clonidine	0.1-2.5 mg/day
N-11	adrenergic stimulant	chlorthalidone	10-50 mg/day
N-12	adrenergic stimulant	guanfacine	0.25-5 mg/day
N-13	adrenergic stimulant	guanabenz	2-40 mg/day
N-14	adrenergic stimulant	trimethaphan	
N-15	alpha/beta adrenergic blocker	carvedilol	6-25 mg bid
N-16	alpha/beta adrenergic blocker	labetalol	10-500 mg/day
N-17	beta adrenergic blocker	propranolol	10-1000 mg/day
N-18	beta adrenergic blocker	metoprolol	10-500 mg/day
N-19	alpha adrenergic blocker	doxazosin	1-16 mg/day
N-20	alpha adrenergic blocker	phentolamine	
N-21	angiotensin converting enzyme inhibitor	quinapril	1-250 mg/day
N-22	angiotensin converting enzyme inhibitor	perindopril erbumine	1-25 mg/day
N-23	angiotensin converting enzyme inhibitor	ramipril	0.25-20 mg/day
N-24	angiotensin converting enzyme inhibitor	captopril	6-50 mg bid or tid
N-25	angiotensin converting enzyme inhibitor	trandolapril	0.25-25 mg/day
N-26	angiotensin converting enzyme inhibitor	fosinopril	2-80 mg/day
N-27	angiotensin converting enzyme inhibitor	lisinopril	1-80 mg/day
N-28	angiotensin converting enzyme inhibitor	moexipril	1-100 mg/day
N-29	angiotensin	enalapril	2.5-40 mg/day

	converting enzyme inhibitor		
N-30	angiotensin converting enzyme inhibitor	benazepril	10-80 mg/day
N-31	angiotensin II receptor antagonist	candesartan cilexetil	2-32 mg/day
N-32	angiotensin II receptor antagonist	inbesartan	
N-33	angiotensin II receptor antagonist	losartan	10-100 mg/day
N-34	angiotensin II receptor antagonist	valsartan	20-600 mg/day
N-35	calcium channel blocker	verapamil	100-600 mg/day
N-36	calcium channel blocker	diltiazem	150-500 mg/day
N-37	calcium channel blocker	nifedipine	1-200 mg/day
N-38	calcium channel blocker	nimodipine	5-500 mg/day
N-39	calcium channel blocker	delodipine	
N-40	calcium channel blocker	nicardipine	1-20 mg/hr i.v.; 5-100 mg/day oral
N-41	calcium channel blocker	isradipine	
N-42	calcium channel blocker	amlodipine	2-10 mg/day
N-43	diuretic	hydrochloro- thiazide	5-100 mg/day
N-44	diuretic	chlorothiazide	250-2000 mg bid or tid
N-45	diuretic	furosemide	5-1000 mg/day
N-46	diuretic	bumetanide	
N-47	diuretic	ethacrynic acid	20-400 mg/day
N-48	diuretic	amiloride	1-20 mg/day
N-49	diuretic	triameterene	
N-50	diuretic	spironolactone	5-1000 mg/day
N-51	diuretic	eplerenone	10-150 mg/day
N-52	vasodilator	hydralazine	5-300 mg/day
N-53	vasodilator	minoxidil	1-100 mg/day
N-54	vasodilator	diazoxide	1-3 mg/kg
N-55	vasodilator	nitroprusside	

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Additional calcium channel blockers which are useful in the combinations of the present invention include, without limitation, those shown in Table 5a.

Table 5a.

Compound Number	Compound Name	Reference
N-56	bepridil	U.S. Patent No. 3,962,238 or U.S. Reissue No. 30,577
N-57	clentiazem	U.S. Patent No. 4,567,175
N-58	diltiazem	U.S. Patent No. 3,562,257
N-59	fendiline	U.S. Patent No. 3,262,977
N-60	gallopamil	U.S. Patent No. 3,261,859
N-61	mibefradil	U.S. Patent No. 4,808,605
N-62	prenylamine	U.S. Patent No. 3,152,173
N-63	semotiadil	U.S. Patent No. 4,786,635
N-64	terodiline	U.S. Patent No. 3,371,014
N-65	verapamil	U.S. Patent No. 3,261,859
N-66	aranipine	U.S. Patent No. 4,572,909
N-67	bamidipine	U.S. Patent No. 4,220,649
N-68	benidipine	European Patent Application Publication No. 106,275
N-69	cilnidipine	U.S. Patent No. 4,672,068
N-70	efonidipine	U.S. Patent No. 4,885,284
N-71	elgodipine	U.S. Patent No. 4,962,592
N-72	felodipine	U.S. Patent No. 4,264,611
N-73	isradipine	U.S. Patent No. 4,466,972
N-74	lacidipine	U.S. Patent No. 4,801,599
N-75	lercanidipine	U.S. Patent No. 4,705,797
N-76	manidipine	U.S. Patent No. 4,892,875
N-77	nicardipine	U.S. Patent No. 3,985,758
N-78	nifendipine	U.S. Patent No. 3,485,847
N-79	nilvadipine	U.S. Patent No. 4,338,322
N-80	nimodipine	U.S. Patent No. 3,799,934
N-81	nisoldipine	U.S. Patent No. 4,154,839
N-82	nitrendipine	U.S. Patent No. 3,799,934
N-83	cinnarizine	U.S. Patent No. 2,882,271

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N-84	flunarizine	U.S. Patent No. 3,773,939
N-85	lidoflazine	U.S. Patent No. 3,267,104
N-86	lomerizine	U.S. Patent No. 4,663,325
N-87	bencyclane	Hungarian Patent No. 151,865
N-88	etafenone	German Patent No. 1,265,758
N-89	perhexiline	British Patent No. 1,025,578

Additional ACE inhibitors which are useful in the combinations of the present invention include, without limitation, those shown in Table 5b.

Table 5b.

Compound Number	Compound Name	Reference
N-90	alacepril	U.S. Patent No. 4,248,883
N-91	benazepril	U.S. Patent No. 4,410,520
N-92	captopril	U.S. Patent Nos. 4,046,889 and 4,105,776
N-93	ceronapril	U.S. Patent No. 4,452,790
N-94	delapril	U.S. Patent No. 4,385,051
N-95	enalapril	U.S. Patent No. 4,374,829
N-96	fosinopril	U.S. Patent No. 4,337,201
N-97	imadapril	U.S. Patent No. 4,508,727
N-98	lisinopril	U.S. Patent No. 4,555,502
N-99	moveltopril	Belgian Patent No. 893,553
N-100	perindopril	U.S. Patent No. 4,508,729
N-101	quinapril	U.S. Patent No. 4,344,949
N-102	ramipril	U.S. Patent No. 4,587,258
N-103	spirapril	U.S. Patent No. 4,470,972
N-104	temocapril	U.S. Patent No. 4,699,905
N-105	trandolapril	U.S. Patent No. 4,933,361

Additional beta andrenergic blockers which are useful in the combinations of the present invention include, without limitation, those shown in Table 5c.

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Table 5c.

Compound Number	Compound Name	Reference
N-106	acebutolol	U.S. Patent No. 3,857,952
N-107	alprenolol	Netherlands Patent Application No. 6,605,692
N-108	amosulalol	U.S. Patent No. 4,217,305
N-109	arotinolol	U.S. Patent No. 3,932,400
N-110	atenolol	U.S. Patent No. 3,663,607 or 3,836,671
N-111	befunolol	U.S. Patent No. 3,853,923
N-112	betaxolol	U.S. Patent No. 4,252,984
N-113	bevantolol	U.S. Patent No. 3,857,981
N-114	bisoprolol	U.S. Patent No. 4,171,370
N-115	bopindolol	U.S. Patent No. 4,340,641
N-116	bucumolol	U.S. Patent No. 3,663,570
N-117	bufetolol	U.S. Patent No. 3,723,476
N-118	bufuralol	U.S. Patent No. 3,929,836
N-119	bunitrolol	U.S. Patent Nos. 3,940,489 and 3,961,071
N-120	buprandolol	U.S. Patent No. 3,309,406
N-121	butiridine hydrochloride	French Patent No. 1,390,056
N-122	butofilolol	U.S. Patent No. 4,252,825
N-123	carazolol	German Patent No. 2,240,599
N-124	carteolol	U.S. Patent No. 3,910,924
N-125	carvedilol	U.S. Patent No. 4,503,067
N-126	celiprolol	U.S. Patent No. 4,034,009
N-127	cetamolol	U.S. Patent No. 4,059,622
N-128	cloranolol	German Patent No. 2,213,044
N-129	dilevalol	Clifton et al., Journal of Medicinal Chemistry, 1982 25, 670
N-130	epanolol	European Patent Publication Application No. 41,491
N-131	indenolol	U.S. Patent No. 4,045,482
N-132	labetalol	U.S. Patent No. 4,012,444
N-133	levobunolol	U.S. Patent No. 4,463,176

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N-134	mepindolol	Seeman et al., Helv. Chim. Acta, 1971, 54, 241
N-135	metipranolol	Czechoslovakian Patent Application No. 128,471
N-136	metoprolol	U.S. Patent No. 3,873,600
N-137	moprolol	U.S. Patent No. 3,501,769
N-138	nadolol	U.S. Patent No. 3,935,267
N-139	nadoxolol	U.S. Patent No. 3,819,702
N-140	nebivalol	U.S. Patent No. 4,654,362
N-141	nipradilol	U.S. Patent No. 4,394,382
N-142	oxprenolol	British Patent No. 1,077,603
N-143	perbutolol	U.S. Patent No. 3,551,493
N-144	pindolol	Swiss Patent Nos. 469,002 and 472,404
N-145	practolol	U.S. Patent No. 3,408,387
N-146	pronethalol	British Patent No. 909,357
N-147	propranolol	U.S. Patent Nos. 3,337,628 and 3,520,919
N-148	sotalol	Uloth et al., Journal of Medicinal Chemistry, 1966, 9, 88
N-149	sufinalol	German Patent No. 2,728,641
N-150	talindol	U.S. Patent Nos. 3,935,259 and 4,038,313
N-151	tertatolol	U.S. Patent No. 3,960,891
N-152	tilisolol	U.S. Patent No. 4,129,565
N-153	timolol	U.S. Patent No. 3,655,663
N-154	toliprolol	U.S. Patent No. 3,432,545
N-155	xibenolol	U.S. Patent No. 4,018,824

Additional alpha andrenergic blockers which are useful in the combinations of the present invention
 5 include, without limitation, those shown in Table 5d.

Table 5d.

Compound Number	Compound Name	Reference
N-156	amosulalol	U.S. Patent No. 4,217,307

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N-157	arotinolol	U.S. Patent No. 3,932,400
N-158	dapiprazole	U.S. Patent No. 4,252,721
N-159	doxazosin	U.S. Patent No. 4,188,390
N-160	fenspiride	U.S. Patent No. 3,399,192
N-161	indoramin	U.S. Patent No. 3,527,761
N-162	labetalol	U.S. Patent No. 4,012,444
N-163	naftopidil	U.S. Patent No. 3,997,666
N-164	nicergoline	U.S. Patent No. 3,228,943
N-165	prazosin	U.S. Patent No. 3,511,836
N-166	tamsulosin	U.S. Patent No. 4,703,063
N-167	tolazoline	U.S. Patent No. 2,161,938
N-168	trimazosin	U.S. Patent No. 3,669,968
N-169	yohimbine	Raymond-Hamet, J. Pharm. Chim., 19, 209 (1934)

Additional angiotensin II receptor antagonists which are useful in the combinations of the present invention include, without limitation, those shown in Table 5e.

Table 5e.

Compound Number	Compound Name	Reference
N-170	candesartan	U.S. Patent No. 5,196,444
N-171	eprosartan	U.S. Patent No. 5,185,351
N-172	irbesartan	U.S. Patent No. 5,270,317
N-173	losartan	U.S. Patent No. 5,138,069
N-174	valsartan	U.S. Patent No. 5,399,578

10 Additional vasodilators which are useful in the combinations of the present invention include, without limitation, those shown in Table 5f.

Table 5f.

Compound Number	Compound Name	Reference
N-175	aluminum	U.S. Patent No. 2,970,082

	nicotinate	7/
N-176	amotriphene	U.S. Patent No. 3,010,965
N-177	bamethan	Corrigan et al., Journal of the American Chemical Society, 1945, 67, 1894
N-178	bencyclane	Hungarian Patent No. 151,865
N-180	bendazol	J. Chem. Soc., 1968, 2426
N-181	benfurodil hemisuccinate	U.S. Patent No. 3,355,463
N-182	benziodarone	U.S. Patent No. 3,012,042
N-183	betahistine	Walter et al.; Journal of the American Chemical Society, 1941, 63, 2771
N-184	bradykinin	Hamburg et al., Arch. Biochem. Biophys., 1958, 76, 252
N-185	brovincamine	U.S. Patent No. 4,146,643
N-186	bufeniode	U.S. Patent No. 3,542,870
N-187	buflomedil	U.S. Patent No. 3,895,030
N-188	butalamine	U.S. Patent No. 3,338,899
N-189	cetiedil	French Patent No. 1,460,571
N-190	chloracizine	British Patent No. 740,932
N-191	chromonar	U.S. Patent No. 3,282,938
N-192	ciclonicate	German Patent No. 1,910,481
N-194	cinepazide	Belgian Patent No. 730,345
N-195	cinnarizine	U.S. Patent No. 2,882,271
N-197	citicoline	Kennedy et al., Journal of the American Chemical Society, 1955, 77, 250 or synthesized as disclosed in Kennedy, Journal of Biological Chemistry, 1956, 222, 185
N-198	clobenfural	British Patent No. 1,160,925
N-199	clonitrate	see Annalen, 1870, 155, 165
N-200	cloricromen	U.S. Patent No. 4,452,811
N-201	cyclandelate	U.S. Patent No. 2,707,193
N-203	diisopropylamine dichloroacetate	Neutralization of dichloroacetic acid with diisopropyl amine
N-204	diisopropylamine dichloroacetate	British Patent No. 862,248
N-205	dilazep	U.S. Patent No. 3,532,685
N-206	dipyridamole	British Patent No. 807,826
N-207	droprenilamine	German Patent No. 2,521,113
N-208	ebumamonine	Hermann et al., Journal of the American Chemical Society, 1979, 101, 1540
N-209	efloxate	British Patent Nos. 803,372

		and 824,547
N-210	eledoisin	British Patent No. 984,810
N-211	erythrityl tetranitrate	May be prepared by nitration of erythritol according to methods well-known to those skilled in the art. See e.g., Merck Index.
N-212	etafenone	German Patent No. 1,265,758
N-213	fasudil	U.S. Patent No. 4,678,783
N-214	fendiline	U.S. Patent No. 3,262,977
N-215	fenoxedil	U.S. Patent No. 3,818,021 or German Patent No. 1,964,712
N-217	floredil	German Patent No. 2,020,464
N-218	flunarizine	German Patent No. 1,929,330 or French Patent No. 2,014,487
N-219	flunarizine	U.S. Patent No. 3,773,939
N-220	ganglefene	U.S.S.R. Patent No. 115,905
N-221	hepronicate	U.S. Patent No. 3,384,642
N-222	hexestrol	U.S. Patent No. 2,357,985
N-223	hexobendine	U.S. Patent No. 3,267,103
N-224	ibudilast	U.S. Patent No. 3,850,941
N-225	ifenprodil	U.S. Patent No. 3,509,164
N-227	iloprost	U.S. Patent No. 4,692,464
N-228	inositol niacinate	Badgett et al., Journal of the American Chemical Society, 1947, 69, 2907
N-229	isoxsuprine	U.S. Patent No. 3,056,836
N-230	itramin tosylate	Swedish Patent No. 168,308
N-231	kallidin	Biochem. Biophys. Res. Commun., 1961, 6, 210
N-232	kallikrein	German Patent No. 1,102,973
N-233	khellin	Baxter et al., Journal of the Chemical Society, 1949, S 30
N-234	lidofiazine	U.S. Patent No. 3,267,104
N-235	lomerizine	U.S. Patent No. 4,663,325
N-236	mannitol hexanitrate	may be prepared by the nitration of mannitol according to methods well-known to those skilled in the art
N-237	medibazine	U.S. Patent No. 3,119,826
N-238	moxisylyte	German Patent No. 905,738
N-239	nafronyl	U.S. Patent No. 3,334,096
N-241	nicametate	Blicke & Jenner, J. Am. Chem. Soc., 64, 1722 (1942)
N-243	nicergoline	U.S. Patent No. 3,228,943
N-245	nicofuranose	Swiss Patent No. 366,523

N-246	nimodipine	U.S. Patent No. 3,799,934
N-247	nitroglycerin	Sobrero, Ann., 64, 398 (1847)
N-248	nylidrin	U.S. Patent Nos. 2,661,372 and 2,661,373
N-249	papaverine	Goldberg, Chem. Prod. Chem. News, 1954, 17, 371
N-250	pentaerythritol tetranitrate	U.S. Patent No. 2,370,437
N-251	pentifylline	German Patent No. 860,217
N-253	pentoxifylline	U.S. Patent No. 3,422,107
N-254	pentritinol	German Patent No. 638,422-3
N-255	perhexilline	British Patent No. 1,025,578
N-256	pimefylline	U.S. Patent No. 3,350,400
N-257	piribedil	U.S. Patent No. 3,299,067
N-258	prenylamine	U.S. Patent No. 3,152,173
N-259	propatyl nitrate	French Patent No. 1,103,113
N-260	prostaglandin E1	may be prepared by any of the methods referenced in the Merck Index, Twelfth Edition, Budavay, Ed., New Jersey, 1996, p. 1353
N-261	suloctidil	German Patent No. 2,334,404
N-262	tinofedrine	U.S. Patent No. 3,563,997
N-263	tolazoline	U.S. Patent No. 2,161,938
N-264	trapidil	East German Patent No. 55,956
N-265	tricromyl	U.S. Patent No. 2,769,015
N-266	trimetazidine	U.S. Patent No. 3,262,852
N-267	trolnitrate phosphate	French Patent No. 984,523 or German Patent No. 830,955
N-268	vincamine	U.S. Patent No. 3,770,724
N-269	vinpocetine	U.S. Patent No. 4,035,750
N-270	viquidil	U.S. Patent No. 2,500,444
N-271	visnadine	U.S. Patent Nos. 2,816,118 and 2,980,699
N-272	xanthinol niacinate	German Patent No. 1,102,750 or Korbonits et al., Acta. Pharm. Hung., 1968, 38, 98

Additional diuretics which are useful in the combinations of the present invention include, without
5 limitation, those shown in Table 5g.

Table 5g.

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Compound Number	Compound Name	Reference
N-273	acetazolamide	U.S. Patent No. 2,980,679
N-274	althiazide	British Patent No. 902,658
N-275	amanozine	Austrian Patent No. 168,063
N-276	ambuside	U.S. Patent No. 3,188,329
N-277	amiloride	Belgian Patent No. 639,386
N-278	arbutin	Tschb&habln, Annalen, 1930, 479, 303
N-279	azosemide	U.S. Patent No. 3,665,002
N-280	bendroflumethiazide	U.S. Patent No. 3,265,573
N-281	benzthiazide	McManus et al., 136th Am. Soc. Meeting (Atlantic City, September 1959). Abstract of Papers, pp 13-0
N-282	benzylhydro-chlorothiazide	U.S. Patent No. 3,108,097
N-283	bumetanide	U.S. Patent No. 3,634,583
N-284	butazolamide	British Patent No. 769,757
N-285	buthiazide	British Patent Nos. 861,367 and 885,078
N-286	chloraminophenamide	U.S. Patent Nos. 2,809,194, 2,965,655 and 2,965,656
N-287	chlorazanyl	Austrian Patent No. 168,063
N-288	chlorothiazide	U.S. Patent Nos. 2,809,194 and 2,937,169
N-289	chlorthalidone	U.S. Patent No. 3,055,904
N-290	clofenamide	Olivier, Rec. Trav. Chim., 1918, 37, 307
N-291	clopamide	U.S. Patent No. 3,459,756
N-292	clorexolone	U.S. Patent No. 3,183,243
N-293	cyclopenthiazide	Belgian Patent No. 587,225
N-294	cyclothiazide	Whitehead et al., Journal of Organic Chemistry, 1961, 26, 2814
N-295	disulfamide	British Patent No. 851,287
N-296	epithiazide	U.S. Patent No. 3,009,911
N-297	ethacrynic acid	U.S. Patent No. 3,255,241
N-298	ethiazide	British Patent No. 861,367
N-299	ethoxolamide	British Patent No. 795,174
N-300	etozolin	U.S. Patent No. 3,072,653
N-301	fenquizone	U.S. Patent No. 3,870,720
N-302	furosemide	U.S. Patent No. 3,058,882
N-303	hydracarbazine	British Patent No. 856,409
N-304	hydrochlorothiazide	U.S. Patent No. 3,164,588
N-305	hydroflumethiazide	U.S. Patent No. 3,254,076
N-306	indapamide	U.S. Patent No. 3,565,911
N-307	isosorbide	U.S. Patent No. 3,160,641

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N-308	mannitol	U.S. Patent No. 2,642,462; or 2,749,371; or 2,759,024
N-309	mefruside	U.S. Patent No. 3,356,692
N-310	methazolamide	U.S. Patent No. 2,783,241
N-311	methyclothiazide	Close et al., Journal of the American Chemical Society, 1960, 82, 1132
N-312	meticrane	French Patent Nos. M2790 and 1,365,504
N-313	metochalcone	Freudenberg et al., Ber., 1957, 90, 957
N-314	metolazone	U.S. Patent No. 3,360,518
N-315	muzolimine	U.S. Patent No. 4,018,890
N-316	paraflutizide	Belgian Patent No. 620,829
N-317	perhexiline	British Patent No. 1,025,578
N-318	piretanide	U.S. Patent No. 4,010,273
N-319	polythiazide	U.S. Patent No. 3,009,911
N-320	quinethazone	U.S. Patent No. 2,976,289
N-321	teclothiazide	Close et al., Journal of the American Chemical Society, 1960, 82, 1132
N-322	ticrynafen	U.S. Patent No. 3,758,506
N-323	torasemide	U.S. Patent No. 4,018,929
N-324	triamterene	U.S. Patent No. 3,081,230
N-325	trichlormethiazide	deStevens et al., Experientia, 1960, 16, 113
N-326	tripamide	Japanese Patent No. 73 05,585
N-327	urea	Can be purchased from commercial sources
N-328	xipamide	U.S. Patent No. 3,567,777

Many of the compounds useful in the present invention
 5 can have at least two asymmetric carbon atoms, and
 therefore include racemates and stereoisomers, such as
 diastereomers and enantiomers, in both pure form and in
 admixture. Such stereoisomers can be prepared using
 conventional techniques, either by reacting enantiomeric
 10 starting materials, or by separating isomers of compounds
 of the present invention.

Isomers may include geometric ⁷⁶isomers, for example cis-isomers or trans-isomers across a double bond. All such isomers are contemplated among the compounds useful in the present invention.

5 The compounds useful in the present invention also include tautomers.

The compounds useful in the present invention as discussed below include their salts, solvates and prodrugs.

10

Dosages, Formulations, and Routes of Administration

The compositions of the present invention can be administered for the prophylaxis and treatment of hyperlipidemic diseases or conditions by any means, preferably oral, that produce contact of these compounds with their site of action in the body, for example in the ileum of a mammal, e.g., a human.

For the prophylaxis or treatment of the conditions referred to above, the compounds useful in the compositions and methods of the present invention can be used as the compound *per se*. Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compound. Such salts must clearly have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention when possible include those derived from inorganic acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, toluenesulfonic, tartaric, and trifluoroacetic acids. The chloride salt is

particularly preferred for medical purposes. Suitable
pharmaceutically acceptable base salts include ammonium
salts, alkali metal salts such as sodium and potassium
salts, and alkaline earth salts such as magnesium and
5 calcium salts.

The anions useful in the present invention are, of
course, also required to be pharmaceutically acceptable
and are also selected from the above list.

The compounds useful in the present invention can be
10 presented with an acceptable carrier in the form of a
pharmaceutical composition. The carrier must, of course,
be acceptable in the sense of being compatible with the
other ingredients of the composition and must not be
deleterious to the recipient. The carrier can be a solid
15 or a liquid, or both, and is preferably formulated with
the compound as a unit-dose composition, for example, a
tablet, which can contain from 0.05% to 95% by weight of
the active compound. Other pharmacologically active
substances can also be present, including other compounds
20 of the present invention. The pharmaceutical compositions
of the invention can be prepared by any of the well known
techniques of pharmacy, consisting essentially of admixing
the components.

These compounds can be administered by any
25 conventional means available for use in conjunction with
pharmaceuticals, either as individual therapeutic
compounds or as a combination of therapeutic compounds.

The amount of compound which is required to achieve
the desired biological effect will, of course, depend on a
30 number of factors such as the specific compound chosen,
the use for which it is intended, the mode of
administration, and the clinical condition of the
recipient.

In general, a total daily⁷⁸ dose of an IBAT inhibitor can be in the range of from about 0.01 to about 1000 mg/day, preferably from about 0.1 mg to about 50 mg/day, more preferably from about 1 to about 10 mg/day.

5 A total daily dose of a fibric acid derivative can generally be in the range of from about 1000 to about 3000 mg/day in single or divided doses. Gemfibrozil or clinofibrate, for example, are frequently each administered separately in a 1200 mg/day dose. Clofibrate
10 is frequently administered in a 2000 mg/day dose. Binifibrate is frequently administered in a 1800 mg/day dose.

Generally a total daily dose of probucol can be in the range of from about 250 to about 2000 mg/day,
15 preferably about 500 to about 1500 mg/day, and more preferably still about 750 to about 1000 mg/day in single or divided doses.

Generally a total daily dose of a nicotinic acid derivative can be in the range of from about 500 to about
20 10,000 mg/day, preferably about 1000 to about 8000 mg/day, and more preferably still about 3000 to about 6000 mg/day in single or divided doses.

For a CETP inhibitor, a daily dose of about 0.01 to about 100 mg/kg body weight/day, and preferably between
25 about 0.5 to about 20 mg/kg body weight/day, may generally be appropriate.

For stanols, a daily dose of about 1000 to about 4000 mg/kg body weight/day, preferably between about 500 to about 1500 mg/kg body weight/day, and more preferably
30 between about 150 to about 600 mg/kg body weight/day will generally be appropriate.

For antihypertensive agents, the daily dose will vary depending on the specific mechanism of activity, the chemistry of the antihypertensive agent, and the patient.

General dose ranges for specific antihypertensive agents are described in Table 5 or in the Biological Assays section.

For cholesterol absorption antagonists, a daily dose of about 0.001 to about 500 mg/kg body weight/day, preferably between about 0.05 to about 300 mg/kg body weight/day, and more preferably between about 1 to about 200 mg/kg body weight/day will generally be appropriate.

For MTP inhibitors, a daily dose of about 0.001 to about 800 mg/kg body weight/day, preferably between about 0.01 to about 500 mg/kg body weight/day, more preferably between about 0.1 to about 300 mg/kg body weight/day, and more preferably still between about 1 to about 200 mg/kg body weight/day will generally be appropriate.

The daily doses described in the preceding paragraphs for the various therapeutic compounds can be administered to the patient in a single dose, or in proportionate multiple subdoses. Subdoses can be administered 2 to 6 times per day. Doses can be in sustained release form effective to obtain desired results.

In the case of pharmaceutically acceptable salts, the weights indicated above refer to the weight of the acid equivalent or the base equivalent of the therapeutic compound derived from the salt.

Oral delivery of the combinations of the present invention can include formulations, as are well known in the art, to provide prolonged or sustained delivery of the drug to the gastrointestinal tract by any number of mechanisms. These include, but are not limited to, pH sensitive release from the dosage form based on the changing pH of the small intestine, slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the formulation, bioadhesion of the dosage form to the mucosal lining of the intestinal tract,

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or enzymatic release of the active drug from the dosage form. For some of the therapeutic compounds useful in the present invention (e.g., IBAT inhibitors or CETP inhibitors), the intended effect is to extend the time
5 period over which the active drug molecule is delivered to the site of action (e.g., the ileum) by manipulation of the dosage form. Thus, enteric-coated and enteric-coated controlled release formulations are within the scope of the present invention. Suitable enteric coatings include
10 cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester.

The combinations of the present invention can be
15 delivered orally either in a solid, in a semi-solid, or in a liquid form. When in a liquid or in a semi-solid form, the combinations of the present invention can, for example, be in the form of a liquid, syrup, or contained in a gel capsule (e.g., a gel cap). In one embodiment,
20 when a CETP inhibitor is used in a combination of the present invention, the CETP inhibitor can be provided in the form of a liquid, syrup, or contained in a gel capsule.

When administered intravenously, the dose for an IBAT
25 inhibitor can, for example, be in the range of from about 0.1 mg/kg body weight to about 1.0 mg/kg body weight, preferably from about 0.25 mg/kg body weight to about 0.75 mg/kg body weight, more preferably from about 0.4 mg/kg body weight to about 0.6 mg/kg body weight.

30 For a CETP inhibitor the intravenously administered dose can, for example, be in the range of from about 0.003 mg/kg body weight to about 1.0 mg/kg body weight, preferably from about 0.01 mg/kg body weight to about 0.75

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mg/kg body weight, more preferably from about 0.1 mg/kg body weight to about 0.6 mg/kg body weight.

When administered intravenously, the dose for a fibric acid derivative can, for example, be in the range of from about 100 mg/kg body weight to about 2000 mg/kg body weight, preferably from about 300 mg/kg body weight to about 1000 mg/kg body weight, more preferably from about 400 mg/kg body weight to about 750 mg/kg body weight.

10 When administered intravenously, the dose for a nicotinic acid derivative can, for example, be in the range of from about 150 mg/kg body weight to about 3000 mg/kg body weight, preferably from about 300 mg/kg body weight to about 2000 mg/kg body weight, more preferably
15 from about 500 mg/kg body weight to about 1000 mg/kg body weight.

The intravenously administered dose for probucol can, for example, be in the range of from about 50 mg/kg body weight to about 1500 mg/kg body weight, preferably from
20 about 100 mg/kg body weight to about 1000 mg/kg body weight, more preferably from about 200 mg/kg body weight to about 750 mg/kg body weight.

The dose of any of these therapeutic compounds can be conveniently administered as an infusion of from about 10
25 ng/kg body weight to about 100 ng/kg body weight per minute. Infusion fluids suitable for this purpose can contain, for example, from about 0.1 ng to about 10 mg, preferably from about 1 ng to about 10 mg per milliliter. Unit doses can contain, for example, from about 1 mg to
30 about 10 g of the compound of the present invention. Thus, ampoules for injection can contain, for example, from about 1 mg to about 100 mg.

Pharmaceutical compositions according to the present invention include those suitable for oral, rectal,

topical, buccal (e.g., sublingual⁸²), and parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound which is being used. In most cases, the preferred route of administration is oral.

Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of at least one therapeutic compound useful in the present invention; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound(s) and the carrier (which can constitute one or more accessory ingredients). In general, the compositions are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet can be prepared by compressing or molding a powder or granules of the compound, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Molded tablets can be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

Pharmaceutical compositions suitable for buccal (sublingual) administration include lozenges comprising a compound of the present invention in a flavored base,

usually sucrose, and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Pharmaceutical compositions suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of the present invention. These preparations are preferably administered intravenously, although administration can also be effected by means of subcutaneous, intramuscular, or intradermal injection.

Such preparations can conveniently be prepared by admixing the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of a compound disclosed herein.

Pharmaceutical compositions suitable for rectal administration are preferably presented as unit-dose suppositories. These can be prepared by admixing a compound of the present invention with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Pharmaceutical compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which can be used include petroleum jelly (e.g., Vaseline), lanolin, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound is generally present at a concentration of from 0.1 to 50% w/w of the composition, for example, from 0.5 to 2%.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such

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patches suitably contain a compound of the present invention in an optionally buffered, aqueous solution, dissolved and/or dispersed in an adhesive, or dispersed in a polymer. A suitable concentration of the active

5 compound is about 1% to 35%, preferably about 3% to 15%.

As one particular possibility, the compound can be delivered from the patch by electrotransport or iontophoresis, for example, as described in Pharmaceutical Research, 3(6), 318 (1986).

10 In any case, the amount of active ingredient that can be combined with carrier materials to produce a single dosage form to be administered will vary depending upon the host treated and the particular mode of administration.

15 The solid dosage forms for oral administration including capsules, tablets, pills, powders, gel caps, and granules noted above comprise one or more compounds useful in the present invention admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage
20 forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate or solubilizing agents such as cyclodextrins. In the case of capsules, tablets, powders, granules, gel caps, and pills, the dosage forms
25 may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents
30 commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

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Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or setting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Pharmaceutically acceptable carriers encompass all the foregoing and the like.

In combination therapy, administration of two or more of the therapeutic agents useful in the present invention may take place sequentially in separate formulations, or may be accomplished by simultaneous administration in a single formulation or separate formulations. Administration may be accomplished by oral route, or by intravenous, intramuscular, or subcutaneous injections. The formulation may be in the form of a bolus, or in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more pharmaceutically-acceptable carriers or diluents, or a binder such as gelatin or hydroxypropylmethyl cellulose, together with one or more of a lubricant, preservative, surface active or dispersing agent.

For oral administration,⁵⁶ the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension, or liquid. Capsules, tablets, etc., can be prepared by conventional methods well known in the art. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient or ingredients. Examples of dosage units are tablets or capsules. These may with advantage contain one or more therapeutic compound in an amount described above. For example, in the case of an IBAT inhibitor, the dose range may be from about 0.01 mg/day to about 500 mg/day or any other dose, dependent upon the specific inhibitor, as is known in the art.

The active ingredients may also be administered by injection as a composition wherein, for example, saline, dextrose, or water may be used as a suitable carrier. A suitable daily dose of each active therapeutic compound is one that achieves the same blood serum level as produced by oral administration as described above.

The therapeutic compounds may further be administered by any combination of oral/oral, oral/parenteral, or parenteral/parenteral route.

Pharmaceutical compositions for use in the treatment methods of the present invention may be administered in oral form or by intravenous administration. Oral administration of the combination therapy is preferred. Dosing for oral administration may be with a regimen calling for single daily dose, or for a single dose every other day, or for multiple, spaced doses throughout the day. The therapeutic compounds which make up the combination therapy may be administered simultaneously, either in a combined dosage form or in separate dosage forms intended for substantially simultaneous oral administration. The therapeutic compounds which make up

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the combination therapy may also be administered sequentially, with either therapeutic compound being administered by a regimen calling for two-step ingestion. Thus, a regimen may call for sequential administration of the therapeutic compounds with spaced-apart ingestion of the separate, active agents. The time period between the multiple ingestion steps may range from a few minutes to several hours, depending upon the properties of each therapeutic compound such as potency, solubility, bioavailability, plasma half-life and kinetic profile of the therapeutic compound, as well as depending upon the effect of food ingestion and the age and condition of the patient. Circadian variation of the target molecule concentration may also determine the optimal dose interval. The therapeutic compounds of the combined therapy whether administered simultaneously, substantially simultaneously, or sequentially, may involve a regimen calling for administration of one therapeutic compound by oral route and another therapeutic compound by intravenous route. Whether the therapeutic compounds of the combined therapy are administered by oral or intravenous route, separately or together, each such therapeutic compound will be contained in a suitable pharmaceutical formulation of pharmaceutically-acceptable excipients, diluents or other formulations components. Examples of suitable pharmaceutically-acceptable formulations containing the therapeutic compounds for oral administration are given above.

30

Treatment Regimen

The dosage regimen to prevent, give relief from, or ameliorate a disease condition having hyperlipemia as an element of the disease, e.g., atherosclerosis, or to protect against or treat further high cholesterol plasma

or blood levels with the compounds and/or compositions of the present invention is selected in accordance with a variety of factors. These include the type, age, weight, sex, diet, and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore deviate from the preferred dosage regimen set forth above.

Initial treatment of a patient suffering from a hyperlipidemic condition can begin with the dosages indicated above. Treatment should generally be continued as necessary over a period of several weeks to several months or years until the hyperlipidemic disease condition has been controlled or eliminated. Patients undergoing treatment with the compounds or compositions disclosed herein can be routinely monitored by, for example, measuring serum LDL and total cholesterol levels by any of the methods well known in the art, to determine the effectiveness of the combination therapy. Continuous analysis of such data permits modification of the treatment regimen during therapy so that optimal effective amounts of each type of therapeutic compound are administered at any point in time, and so that the duration of treatment can be determined as well. In this way, the treatment regimen/dosing schedule can be rationally modified over the course of therapy so that the lowest amount of the therapeutic compounds which together exhibit satisfactory effectiveness is administered, and so that administration is continued only so long as is

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necessary to successfully treat the hyperlipidemic condition.

A potential advantage of the combination disclosed herein may be reduction of the amount of any individual therapeutic compound, or all therapeutic compounds, effective in treating hyperlipidemic conditions such as atherosclerosis and hypercholesterolemia.

One of the several embodiments of the present invention provides a combination comprising the use of a first amount of an IBAT inhibitor and a second amount of another cardiovascular therapeutic useful in the prophylaxis or treatment of hyperlipidemia or atherosclerosis, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds. For example one of the many embodiments of the present invention is a combination therapy comprising therapeutic dosages of an IBAT inhibitor and a CETP inhibitor. A preferred embodiment of the present invention is a combination therapy comprising therapeutic dosages of a benzothiepine IBAT inhibitor and a CETP inhibitor.

In another embodiment, the invention comprises a combination therapy comprising a first amount of an IBAT inhibitor and a second amount of a fibric acid derivative, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds. Still another embodiment comprises a combination therapy comprising a first amount of an IBAT inhibitor and a second amount of a nicotinic acid derivative, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of

the compounds. The IBAT inhibitor⁹⁰ in the embodiments of this paragraph is preferably a benzothiepine IBAT inhibitor.

Alternatively, an embodiment of the present invention
5 provides a combination which comprises a first amount of a CETP inhibitor and a second amount of another cardiovascular therapeutic, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition
10 effective amount of the compounds. A preferred embodiment provides a combination comprising a first amount of a CETP inhibitor and a second amount of a fibric acid derivative, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-
15 atherosclerotic condition effective amount of the compounds. The invention is also embodied in a therapeutic composition comprising first amount of a CETP inhibitor and a second amount of a nicotinic acid derivative, wherein the first and second amounts together
20 comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds. In the embodiments described in this paragraph, the CETP inhibitor is preferably the compound of formula C-1.

25 In another of its many embodiments, the present invention provides a combination comprising therapeutic dosages of an IBAT inhibitor and a phytosterol. In a preferred embodiment, the present invention provides a combination therapy comprising therapeutic dosages of a
30 benzothiepine IBAT inhibitor and a phytosterol. In another preferred embodiment, the present invention provides a combination therapy comprising therapeutic dosages of an IBAT inhibitor and a stanol.

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In another of its many embodiments, the present invention provides a combination comprising a first amount of an IBAT inhibitor and a second amount of a fibric acid derivative, wherein the first and second amounts together
5 comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds. In a preferred embodiment, the IBAT inhibitor is a benzothiepine IBAT inhibitor. In another preferred embodiment, the IBAT inhibitor is a
10 benzothiazepine IBAT inhibitor. In yet another preferred embodiment, the IBAT inhibitor is a naphthalene IBAT inhibitor.

In another of its many embodiments, the present invention provides a combination comprising therapeutic
15 dosages of an IBAT inhibitor and a cholesterol absorption antagonist. In a preferred embodiment, the present invention provides a combination therapy comprising therapeutic dosages of a benzothiepine IBAT inhibitor and a cholesterol absorption antagonist.

20 The embodiments of the present invention can comprise a combination therapy using two or more of the therapeutic compounds described or incorporated herein. The combination therapy can comprise two or more therapeutic compounds from different classes of chemistry, e.g., IBAT
25 inhibitors can be therapeutically combined with CETP inhibitors. Therapeutic combinations can comprise more than two therapeutic compounds. For example, two or more therapeutic compounds from the same class of chemistry can comprise the therapy, e.g. a combination therapy
30 comprising two or more IBAT inhibitors or two or more CETP inhibitors. In another embodiment the present invention provides a combination comprising two or more IBAT inhibitors or two or more stanols.

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A further embodiment of the instant invention comprises the use of any of the cardiovascular combination therapies described herein for the prophylaxis or treatment of hypercholesterolemia or atherosclerosis.

5 The following non-limiting examples serve to illustrate various aspects of the present invention.

c. Examples

10 Table 6 illustrates examples of some of the many combinations of the present invention wherein the combination comprises a first amount of IBAT inhibitor and a second amount of a CETP inhibitor, wherein the first and second amounts together comprise an anti-hyperlipidemic

15 condition effective amount or an anti-atherosclerotic condition effective amount of the compounds.

Table 6

Example Number	Component 1	Component 2
1	B-1	C-1
2	B-1	C-2
3	B-1	C-3
4	B-1	C-4
5	B-1	C-5
6	B-1	C-6
7	B-1	C-7
8	B-1	C-8
9	B-1	C-9
10	B-1	C-10
11	B-1	C-11
12	B-1	C-12
13	B-1	C-13
14	B-1	C-14
15	B-1	C-15
16	B-1	C-16
17	B-1	C-17

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18	B-1	C-18
19	B-1	C-19
20	B-1	C-20
21	B-2	C-1
22	B-2	C-2
23	B-2	C-3
24	B-2	C-4
25	B-2	C-5
26	B-2	C-6
27	B-2	C-7
28	B-2	C-8
29	B-2	C-9
30	B-2	C-10
31	B-2	C-11
32	B-2	C-12
33	B-2	C-13
34	B-2	C-14
35	B-2	C-15
36	B-2	C-16
37	B-2	C-17
38	B-2	C-18
39	B-2	C-19
40	B-2	C-20
41	B-3	C-1
42	B-3	C-2
43	B-3	C-3
44	B-3	C-4
45	B-3	C-5
46	B-3	C-6
47	B-3	C-7
48	B-3	C-8
49	B-3	C-9
50	B-3	C-10
51	B-3	C-11
52	B-3	C-12
53	B-3	C-13
54	B-3	C-14
55	B-3	C-15
56	B-3	C-16
57	B-3	C-17
58	B-3	C-18

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59	B-3	C-19
60	B-3	C-20
61	B-4	C-1
62	B-4	C-2
63	B-4	C-3
64	B-4	C-4
65	B-4	C-5
66	B-4	C-6
67	B-4	C-7
68	B-4	C-8
69	B-4	C-9
70	B-4	C-10
71	B-4	C-11
72	B-4	C-12
73	B-4	C-13
74	B-4	C-14
75	B-4	C-15
76	B-4	C-16
77	B-4	C-17
78	B-4	C-18
79	B-4	C-19
80	B-4	C-20
81	B-5	C-1
82	B-5	C-2
83	B-5	C-3
84	B-5	C-4
85	B-5	C-5
86	B-5	C-6
87	B-5	C-7
88	B-5	C-8
89	B-5	C-9
90	B-5	C-10
91	B-5	C-11
92	B-5	C-12
93	B-5	C-13
94	B-5	C-14
95	B-5	C-15
96	B-5	C-16
97	B-5	C-17
98	B-5	C-18
99	B-5	C-19

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100	B-5	C-20
101	B-6	C-1
102	B-6	C-2
103	B-6	C-3
104	B-6	C-4
105	B-6	C-5
106	B-6	C-6
107	B-6	C-7
108	B-6	C-8
109	B-6	C-9
110	B-6	C-10
111	B-6	C-11
112	B-6	C-12
113	B-6	C-13
114	B-6	C-14
115	B-6	C-15
116	B-6	C-16
117	B-6	C-17
118	B-6	C-18
119	B-6	C-19
120	B-6	C-20
121	B-7	C-1
122	B-7	C-2
123	B-7	C-3
124	B-7	C-4
125	B-7	C-5
126	B-7	C-6
127	B-7	C-7
128	B-7	C-8
129	B-7	C-9
130	B-7	C-10
131	B-7	C-11
132	B-7	C-12
133	B-7	C-13
134	B-7	C-14
135	B-7	C-15
136	B-7	C-16
137	B-7	C-17
138	B-7	C-18
139	B-7	C-19
140	B-7	C-20

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141	B-8	C-1
142	B-8	C-2
143	B-8	C-3
144	B-8	C-4
145	B-8	C-5
146	B-8	C-6
147	B-8	C-7
148	B-8	C-8
149	B-8	C-9
150	B-8	C-10
151	B-8	C-11
152	B-8	C-12
153	B-8	C-13
154	B-8	C-14
155	B-8	C-15
156	B-8	C-16
157	B-8	C-17
158	B-8	C-18
159	B-8	C-19
160	B-8	C-20
161	B-9	C-1
162	B-9	C-2
163	B-9	C-3
164	B-9	C-4
165	B-9	C-5
166	B-9	C-6
167	B-9	C-7
168	B-9	C-8
169	B-9	C-9
170	B-9	C-10
171	B-9	C-11
172	B-9	C-12
173	B-9	C-13
174	B-9	C-14
175	B-9	C-15
176	B-9	C-16
177	B-9	C-17
178	B-9	C-18
179	B-9	C-19
180	B-9	C-20
181	B-10	C-1

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182	B-10	C-2
183	B-10	C-3
184	B-10	C-4
185	B-10	C-5
186	B-10	C-6
187	B-10	C-7
188	B-10	C-8
189	B-10	C-9
190	B-10	C-10
191	B-10	C-11
192	B-10	C-12
193	B-10	C-13
194	B-10	C-14
195	B-10	C-15
196	B-10	C-16
197	B-10	C-17
198	B-10	C-18
199	B-10	C-19
200	B-10	C-20
201	B-11	C-1
202	B-11	C-2
203	B-11	C-3
204	B-11	C-4
205	B-11	C-5
206	B-11	C-6
207	B-11	C-7
208	B-11	C-8
209	B-11	C-9
210	B-11	C-10
211	B-11	C-11
212	B-11	C-12
213	B-11	C-13
214	B-11	C-14
215	B-11	C-15
216	B-11	C-16
217	B-11	C-17
218	B-11	C-18
219	B-11	C-19
220	B-11	C-20
221	B-12	C-1
222	B-12	C-2

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223	B-12	C-3
224	B-12	C-4
225	B-12	C-5
226	B-12	C-6
227	B-12	C-7
228	B-12	C-8
229	B-12	C-9
230	B-12	C-10
231	B-12	C-11
232	B-12	C-12
233	B-12	C-13
234	B-12	C-14
235	B-12	C-15
236	B-12	C-16
237	B-12	C-17
238	B-12	C-18
239	B-12	C-19
240	B-12	C-20
241	B-13	C-1
242	B-13	C-2
243	B-13	C-3
244	B-13	C-4
245	B-13	C-5
246	B-13	C-6
247	B-13	C-7
248	B-13	C-8
249	B-13	C-9
250	B-13	C-10
251	B-13	C-11
252	B-13	C-12
253	B-13	C-13
254	B-13	C-14
255	B-13	C-15
256	B-13	C-16
257	B-13	C-17
258	B-13	C-18
259	B-13	C-19
260	B-13	C-20
261	B-14	C-1
262	B-14	C-2
263	B-14	C-3

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264	B-14	C-4
265	B-14	C-5
266	B-14	C-6
267	B-14	C-7
268	B-14	C-8
269	B-14	C-9
270	B-14	C-10
271	B-14	C-11
272	B-14	C-12
273	B-14	C-13
274	B-14	C-14
275	B-14	C-15
276	B-14	C-16
277	B-14	C-17
278	B-14	C-18
279	B-14	C-19
280	B-14	C-20
281	B-15	C-1
282	B-15	C-2
283	B-15	C-3
284	B-15	C-4
285	B-15	C-5
286	B-15	C-6
287	B-15	C-7
288	B-15	C-8
289	B-15	C-9
290	B-15	C-10
291	B-15	C-11
292	B-15	C-12
293	B-15	C-13
294	B-15	C-14
295	B-15	C-15
296	B-15	C-16
297	B-15	C-17
298	B-15	C-18
299	B-15	C-19
300	B-15	C-20
301	B-16	C-1
302	B-16	C-2
303	B-16	C-3
304	B-16	C-4

100

305	B-16	C-5
306	B-16	C-6
307	B-16	C-7
308	B-16	C-8
309	B-16	C-9
310	B-16	C-10
311	B-16	C-11
312	B-16	C-12
313	B-16	C-13
314	B-16	C-14
315	B-16	C-15
316	B-16	C-16
317	B-16	C-17
318	B-16	C-18
319	B-16	C-19
320	B-16	C-20
321	B-17	C-1
322	B-17	C-2
323	B-17	C-3
324	B-17	C-4
325	B-17	C-5
326	B-17	C-6
327	B-17	C-7
328	B-17	C-8
329	B-17	C-9
330	B-17	C-10
331	B-17	C-11
332	B-17	C-12
333	B-17	C-13
334	B-17	C-14
335	B-17	C-15
336	B-17	C-16
337	B-17	C-17
338	B-17	C-18
339	B-17	C-19
340	B-17	C-20
341	B-18	C-1
342	B-18	C-2
343	B-18	C-3
344	B-18	C-4
345	B-18	C-5

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346	B-18	C-6
347	B-18	C-7
348	B-18	C-8
349	B-18	C-9
350	B-18	C-10
351	B-18	C-11
352	B-18	C-12
353	B-18	C-13
354	B-18	C-14
355	B-18	C-15
356	B-18	C-16
357	B-18	C-17
358	B-18	C-18
359	B-18	C-19
360	B-18	C-20
361	B-19	C-1
362	B-19	C-2
363	B-19	C-3
364	B-19	C-4
365	B-19	C-5
366	B-19	C-6
367	B-19	C-7
368	B-19	C-8
369	B-19	C-9
370	B-19	C-10
371	B-19	C-11
372	B-19	C-12
373	B-19	C-13
374	B-19	C-14
375	B-19	C-15
376	B-19	C-16
377	B-19	C-17
378	B-19	C-18
379	B-19	C-19
380	B-19	C-20
381	B-20	C-1
382	B-20	C-2
383	B-20	C-3
384	B-20	C-4
385	B-20	C-5
386	B-20	C-6

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387	B-20	C-7
388	B-20	C-8
389	B-20	C-9
390	B-20	C-10
391	B-20	C-11
392	B-20	C-12
393	B-20	C-13
394	B-20	C-14
395	B-20	C-15
396	B-20	C-16
397	B-20	C-17
398	B-20	C-18
399	B-20	C-19
400	B-20	C-20

Table 8 illustrates examples of some combinations of the present invention wherein the combination comprises a first amount of an IBAT inhibitor and a second amount of a fibric acid derivative, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds.

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Table 8.

Example Number	Component 1	Component 2
601	B-1	clofibrate
602	B-2	clofibrate
603	B-3	clofibrate
604	B-4	clofibrate
605	B-5	clofibrate
606	B-6	clofibrate
607	B-7	clofibrate
608	B-8	clofibrate
609	B-9	clofibrate
610	B-10	clofibrate
611	B-11	clofibrate
612	B-12	clofibrate
613	B-13	clofibrate
614	B-14	clofibrate
615	B-15	clofibrate
616	B-16	clofibrate
617	B-17	clofibrate
618	B-18	clofibrate
619	B-19	clofibrate
620	B-20	clofibrate
621	B-1	fenofibrate
622	B-2	fenofibrate
623	B-3	fenofibrate
624	B-4	fenofibrate
625	B-5	fenofibrate
626	B-6	fenofibrate
627	B-7	fenofibrate
628	B-8	fenofibrate
629	B-9	fenofibrate
630	B-10	fenofibrate
631	B-11	fenofibrate
632	B-12	fenofibrate
633	B-13	fenofibrate
634	B-14	fenofibrate
635	B-15	fenofibrate
636	B-16	fenofibrate
637	B-17	fenofibrate

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638	B-18	fenofibrate
639	B-19	fenofibrate
640	B-20	fenofibrate
641	B-1	ciprofibrate
642	B-2	ciprofibrate
643	B-3	ciprofibrate
644	B-4	ciprofibrate
645	B-5	ciprofibrate
646	B-6	ciprofibrate
647	B-7	ciprofibrate
648	B-8	ciprofibrate
649	B-9	ciprofibrate
650	B-10	ciprofibrate
651	B-11	ciprofibrate
652	B-12	ciprofibrate
653	B-13	ciprofibrate
654	B-14	ciprofibrate
655	B-15	ciprofibrate
656	B-16	ciprofibrate
657	B-17	ciprofibrate
658	B-18	ciprofibrate
659	B-19	ciprofibrate
660	B-20	ciprofibrate
661	B-1	bezafibrate
662	B-2	bezafibrate
663	B-3	bezafibrate
664	B-4	bezafibrate
665	B-5	bezafibrate
666	B-6	bezafibrate
667	B-7	bezafibrate
668	B-8	bezafibrate
669	B-9	bezafibrate
670	B-10	bezafibrate
671	B-11	bezafibrate
672	B-12	bezafibrate
673	B-13	bezafibrate
674	B-14	bezafibrate
675	B-15	bezafibrate
676	B-16	bezafibrate
677	B-17	bezafibrate
678	B-18	bezafibrate

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679	B-19	bezafibrate
680	B-20	bezafibrate
681	B-1	gemfibrozil
682	B-2	gemfibrozil
683	B-3	gemfibrozil
684	B-4	gemfibrozil
685	B-5	gemfibrozil
686	B-6	gemfibrozil
687	B-7	gemfibrozil
688	B-8	gemfibrozil
689	B-9	gemfibrozil
690	B-10	gemfibrozil
691	B-11	gemfibrozil
692	B-12	gemfibrozil
693	B-13	gemfibrozil
694	B-14	gemfibrozil
695	B-15	gemfibrozil
696	B-16	gemfibrozil
697	B-17	gemfibrozil
698	B-18	gemfibrozil
699	B-19	gemfibrozil
700	B-20	gemfibrozil

Table 10 illustrates examples of some combinations of the present invention wherein the combination comprises a first amount of an IBAT inhibitor and a second amount of a
 5 nicotinic acid derivative, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds.

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Table 10.

Example Number	Component 1	Component 2
901	B-1	nicotinic acid (niacin)
902	B-2	nicotinic acid (niacin)
903	B-3	nicotinic acid (niacin)
904	B-4	nicotinic acid (niacin)
905	B-5	nicotinic acid (niacin)
906	B-6	nicotinic acid (niacin)
907	B-7	nicotinic acid (niacin)
908	B-8	nicotinic acid (niacin)
909	B-9	nicotinic acid (niacin)
910	B-10	nicotinic acid (niacin)
911	B-11	nicotinic acid (niacin)
912	B-12	nicotinic acid (niacin)
913	B-13	nicotinic acid (niacin)
914	B-14	nicotinic acid (niacin)
915	B-15	nicotinic acid (niacin)
916	B-16	nicotinic acid (niacin)
917	B-17	nicotinic acid (niacin)
918	B-18	nicotinic acid (niacin)
919	B-19	nicotinic acid (niacin)
920	B-20	nicotinic acid (niacin)
921	B-1	niceritrol
922	B-2	niceritrol
923	B-3	niceritrol
924	B-4	niceritrol
925	B-5	niceritrol
926	B-6	niceritrol
927	B-7	niceritrol
928	B-8	niceritrol
929	B-9	niceritrol
930	B-10	niceritrol
931	B-11	niceritrol
932	B-12	niceritrol
933	B-13	niceritrol
934	B-14	niceritrol
935	B-15	niceritrol
936	B-16	niceritrol
937	B-17	niceritrol

938	B-18	niceritrol
939	B-19	niceritrol
940	B-20	niceritrol
941	B-1	acipimox
942	B-2	acipimox
943	B-3	acipimox
944	B-4	acipimox
945	B-5	acipimox
946	B-6	acipimox
947	B-7	acipimox
948	B-8	acipimox
949	B-9	acipimox
950	B-10	acipimox
951	B-11	acipimox
952	B-12	acipimox
953	B-13	acipimox
954	B-14	acipimox
955	B-15	acipimox
956	B-16	acipimox
957	B-17	acipimox
958	B-18	acipimox
959	B-19	acipimox
960	B-20	acipimox

Table 13 illustrates examples of some combinations of the present invention wherein the combination comprises a first amount of a CETP inhibitor and a second amount of a fibric acid derivative, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds.

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Table 13.

Example Number	Component 1	Component 2
5601	C-1	clofibrate
5602	C-2	clofibrate
5603	C-3	clofibrate
5604	C-4	clofibrate
5605	C-5	clofibrate
5606	C-6	clofibrate
5607	C-7	clofibrate
5608	C-8	clofibrate
5609	C-9	clofibrate
5610	C-10	clofibrate
5611	C-11	clofibrate
5612	C-12	clofibrate
5613	C-13	clofibrate
5614	C-14	clofibrate
5615	C-15	clofibrate
5616	C-16	clofibrate
5617	C-17	clofibrate
5618	C-18	clofibrate
5619	C-19	clofibrate
5620	C-20	clofibrate
5621	C-1	fenofibrate
5622	C-2	fenofibrate
5623	C-3	fenofibrate
5624	C-4	fenofibrate
5625	C-5	fenofibrate
5626	C-6	fenofibrate
5627	C-7	fenofibrate
5628	C-8	fenofibrate
5629	C-9	fenofibrate
5630	C-10	fenofibrate
5631	C-11	fenofibrate
5632	C-12	fenofibrate
5633	C-13	fenofibrate
5634	C-14	fenofibrate
5635	C-15	fenofibrate
5636	C-16	fenofibrate
5637	C-17	fenofibrate

5638	C-18	fenofibrate
5639	C-19	fenofibrate
5640	C-20	fenofibrate
5641	C-1	ciprofibrate
5642	C-2	ciprofibrate
5643	C-3	ciprofibrate
5644	C-4	ciprofibrate
5645	C-5	ciprofibrate
5646	C-6	ciprofibrate
5647	C-7	ciprofibrate
5648	C-8	ciprofibrate
5649	C-9	ciprofibrate
5650	C-10	ciprofibrate
5651	C-11	ciprofibrate
5652	C-12	ciprofibrate
5653	C-13	ciprofibrate
5654	C-14	ciprofibrate
5655	C-15	ciprofibrate
5656	C-16	ciprofibrate
5657	C-17	ciprofibrate
5658	C-18	ciprofibrate
5659	C-19	ciprofibrate
5660	C-20	ciprofibrate
5661	C-1	bezafibrate
5662	C-2	bezafibrate
5663	C-3	bezafibrate
5664	C-4	bezafibrate
5665	C-5	bezafibrate
5666	C-6	bezafibrate
5667	C-7	bezafibrate
5668	C-8	bezafibrate
5669	C-9	bezafibrate
5670	C-10	bezafibrate
5671	C-11	bezafibrate
5672	C-12	bezafibrate
5673	C-13	bezafibrate
5674	C-14	bezafibrate
5675	C-15	bezafibrate
5676	C-16	bezafibrate
5677	C-17	bezafibrate
5678	C-18	bezafibrate

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5679	C-19	bezafibrate
5680	C-20	bezafibrate
5681	C-1	gemfibrozil
5682	C-2	gemfibrozil
5683	C-3	gemfibrozil
5684	C-4	gemfibrozil
5685	C-5	gemfibrozil
5686	C-6	gemfibrozil
5687	C-7	gemfibrozil
5688	C-8	gemfibrozil
5689	C-9	gemfibrozil
5690	C-10	gemfibrozil
5691	C-11	gemfibrozil
5692	C-12	gemfibrozil
5693	C-13	gemfibrozil
5694	C-14	gemfibrozil
5695	C-15	gemfibrozil
5696	C-16	gemfibrozil
5697	C-17	gemfibrozil
5698	C-18	gemfibrozil
5699	C-19	gemfibrozil
5700	C-20	gemfibrozil

Table 15 illustrates examples of some combinations of the present invention wherein the combination comprises a first amount of a CETP inhibitor and a second amount of a 5 nicotinic acid derivative, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount or an anti-atherosclerotic condition effective amount of the compounds.

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Table 15.

Example Number	Component 1	Component 2
5901	C-1	nicotinic acid (niacin)
5902	C-2	nicotinic acid (niacin)
5903	C-3	nicotinic acid (niacin)
5904	C-4	nicotinic acid (niacin)

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5905	C-5	nicotinic acid (niacin)
5906	C-6	nicotinic acid (niacin)
5907	C-7	nicotinic acid (niacin)
5908	C-8	nicotinic acid (niacin)
5909	C-9	nicotinic acid (niacin)
5910	C-10	nicotinic acid (niacin)
5911	C-11	nicotinic acid (niacin)
5912	C-12	nicotinic acid (niacin)
5913	C-13	nicotinic acid (niacin)
5914	C-14	nicotinic acid (niacin)
5915	C-15	nicotinic acid (niacin)
5916	C-16	nicotinic acid (niacin)
5917	C-17	nicotinic acid (niacin)
5918	C-18	nicotinic acid (niacin)
5919	C-19	nicotinic acid (niacin)
5920	C-20	nicotinic acid (niacin)
5921	C-1	niceritrol
5922	C-2	niceritrol
5923	C-3	niceritrol
5924	C-4	niceritrol
5925	C-5	niceritrol
5926	C-6	niceritrol
5927	C-7	niceritrol
5928	C-8	niceritrol
5929	C-9	niceritrol
5930	C-10	niceritrol
5931	C-11	niceritrol
5932	C-12	niceritrol
5933	C-13	niceritrol
5934	C-14	niceritrol
5935	C-15	niceritrol
5936	C-16	niceritrol
5937	C-17	niceritrol
5938	C-18	niceritrol
5939	C-19	niceritrol
5940	C-20	niceritrol
5941	C-1	acipimox
5942	C-2	acipimox
5943	C-3	acipimox
5944	C-4	acipimox
5945	C-5	acipimox

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5946	C-6	acipimox
5947	C-7	acipimox
5948	C-8	acipimox
5949	C-9	acipimox
5950	C-10	acipimox
5951	C-11	acipimox
5952	C-12	acipimox
5953	C-13	acipimox
5954	C-14	acipimox
5955	C-15	acipimox
5956	C-16	acipimox
5957	C-17	acipimox
5958	C-18	acipimox
5959	C-19	acipimox
5960	C-20	acipimox

Any of the MTP inhibitor compounds described by Wetterau et al. (Id.) can be used in combinations of the present invention wherein the combination comprises a first amount of an ileal bile acid transporter inhibiting compound and a second amount of a MTP inhibitor wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, an anti-hypercholesterolemic condition effective amount, or an anti-hypertensive condition effective amount of the compounds. The IBAT inhibitor in the embodiments of this invention is preferably a benzothiepine IBAT inhibitor.

In another preferred embodiment, the IBAT inhibitor is a benzothiazepine IBAT inhibitor. In still another preferred embodiment, the IBAT inhibitor is a naphthalene IBAT inhibitor. The IBAT inhibitor can, without limitation, be any one or combination of the compounds listed in Table 1.

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Table 17 illustrates examples of some combinations of the present invention wherein the combination comprises a first amount of an ileal bile acid transporter inhibiting compound and a second amount of a cholesterol absorption antagonist wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, an anti-hypercholesterolemic condition effective amount, or an anti-hypertensive condition effective amount of the compounds. The IBAT inhibitor in the embodiments of this invention is preferably a benzothiepine IBAT inhibitor. In another preferred embodiment, the IBAT inhibitor is a benzothiazepine IBAT inhibitor. In still another preferred embodiment, the IBAT inhibitor is a naphthalene IBAT inhibitor. The IBAT inhibitor can, without limitation, be any one or combination of the compounds listed in Table 1. Preferably the cholesterol absorption antagonist is an azetidinone compound, and more preferably the cholesterol absorption antagonist is compound A-1.

Table 16.

Example Number	Compound 1	Compound 2
7001	B-1	A-1
7002	B-2	A-1
7003	B-3	A-1
7004	B-4	A-1
7005	B-5	A-1
7006	B-6	A-1
7007	B-7	A-1
7008	B-8	A-1
7009	B-9	A-1
7010	B-10	A-1
7011	B-11	A-1
7012	B-12	A-1
7013	B-13	A-1

7014	B-14	A-1
7015	B-15	A-1
7016	B-16	A-1
7017	B-17	A-1
7018	B-18	A-1
7019	B-19	A-1
7020	B-20	A-1
7021	B-21	A-1
7022	B-22	A-1
7023	B-23	A-1
7024	B-24	A-1
7025	B-25	A-1
7026	B-26	A-1
7027	B-27	A-1
7028	B-28	A-1
7029	B-29	A-1
7030	B-30	A-1
7031	B-31	A-1
7032	B-32	A-1
7033	B-33	A-1
7034	B-34	A-1
7035	B-35	A-1
7036	B-36	A-1
7037	B-37	A-1
7038	B-38	A-1
7039	B-39	A-1

Table 21 illustrates examples of some combinations of the present invention wherein the combination comprises a first amount of an ileal bile acid transporter inhibiting compound and a second amount of a cardiovascular therapeutic useful in the prophylaxis or treatment of hypertension, wherein the first and second amounts together comprise an anti-hyperlipidemic condition effective amount, an anti-atherosclerotic condition effective amount, an anti-hypercholesterolemic condition effective amount, or an anti-hypertensive condition effective amount of the compounds. The IBAT inhibitor in the embodiments of this invention is preferably a benzothiepine IBAT inhibitor. In another preferred embodiment, the IBAT inhibitor is a benzothiazepine IBAT

inhibitor. In still another ¹¹⁵ preferred embodiment, the IBAT inhibitor is a naphthalene IBAT inhibitor. The IBAT inhibitor can, without limitation, be any one or combination of the compounds listed in Table 1.

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Table 21.

Example Number	Compound 1	Compound 2
12000	amiloride	B-1
12001	amlodipine	B-1
12002	benazepril	B-1
12003	bumetanide	B-1
12004	candesartan cilexetil	B-1
12005	captopril	B-1
12006	carvedilol	B-1
12007	chlorothiazide	B-1
12008	chlorthalidone	B-1
12009	clonidine	B-1
12010	delodipine	B-1
12011	diazoxide	B-1
12012	diltiazem	B-1
12013	doxazosin	B-1
12014	enalapril	B-1
12015	eplerenone	B-1
12016	ethacrynic acid	B-1
12017	fosinopril	B-1
12018	furosemide	B-1
12019	guanabenz	B-1
12020	guanadrel	B-1
12021	guanethidine	B-1
12022	guanfacine	B-1
12023	hydralazine	B-1
12024	hydrochlorothiazide	B-1
12025	inbesartan	B-1
12026	isradipine	B-1
12027	labetalol	B-1
12028	lisinopril	B-1
12029	losartan	B-1
12030	methyldopa	B-1
12031	methyldopate	B-1
12032	metoprolol	B-1
12033	minoxidil	B-1
12034	moexipril	B-1
12035	nicardipine	B-1
12036	nifedipine	B-1

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12037	nimodipine	B-1
12038	nitroprusside	B-1
12039	perindopril erbumine	B-1
12040	phenoxybenzamine	B-1
12041	phentolamine	B-1
12042	polythiazide	B-1
12043	prazosin	B-1
12044	propranolol	B-1
12045	quinapril	B-1
12046	ramipril	B-1
12047	reserpine	B-1
12048	spironolactone	B-1
12049	terazosin	B-1
12050	trandolapril	B-1
12051	triameterene	B-1
12052	trimethaphan	B-1
12053	valsartan	B-1
12054	verapamil	B-1
12055	amiloride	B-2
12056	amlodipine	B-2
12057	benazepril	B-2
12058	bumetanide	B-2
12059	candesartan cilexetil	B-2
12060	captopril	B-2
12061	carvedilol	B-2
12062	chlorothiazide	B-2
12063	chlorthalidone	B-2
12064	clonidine	B-2
12065	delodipine	B-2
12066	diazoxide	B-2
12067	diltiazem	B-2
12068	doxazosin	B-2
12069	enalapril	B-2
12070	eplerenone	B-2
12071	ethacrynic acid	B-2
12072	fosinopril	B-2
12073	furosemide	B-2
12074	guanabenz	B-2
12075	guanadrel	B-2
12076	guanethidine	B-2
12077	guanfacine	B-2
12078	hydralazine	B-2
12079	hydrochlorothiazide	B-2
12080	inbesartan	B-2
12081	isradipine	B-2
12082	labetalol	B-2
12083	lisinopril	B-2
12084	losartan	B-2

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12085	methyldopa	B-2
12086	methyldopate	B-2
12087	metoprolol	B-2
12088	minoxidil	B-2
12089	moexipril	B-2
12090	nicardipine	B-2
12091	nifedipine	B-2
12092	nimodipine	B-2
12093	nitroprusside	B-2
12094	perindopril erbumine	B-2
12095	phenoxybenzamine	B-2
12096	phentolamine	B-2
12097	polythiazide	B-2
12098	prazosin	B-2
12099	propranolol	B-2
12100	quinapril	B-2
12101	ramipril	B-2
12102	reserpine	B-2
12103	spironolactone	B-2
12104	terazosin	B-2
12105	trandolapril	B-2
12106	triameterene	B-2
12107	trimethaphan	B-2
12108	valsartan	B-2
12109	verapamil	B-2
12110	amiloride	B-3
12111	amlodipine	B-3
12112	benazepril	B-3
12113	bumetanide	B-3
12114	candesartan cilexetil	B-3
12115	captopril	B-3
12116	carvedilol	B-3
12117	chlorothiazide	B-3
12118	chlorthalidone	B-3
12119	clonidine	B-3
12120	delodipine	B-3
12121	diazoxide	B-3
12122	diltiazem	B-3
12123	doxazosin	B-3
12124	enalapril	B-3
12125	eplerenone	B-3
12126	ethacrynic acid	B-3
12127	fosinopril	B-3
12128	furosemide	B-3
12129	guanabenz	B-3
12130	guanadrel	B-3
12131	guanethidine	B-3
12132	guanfacine	B-3

12133	hydralazine	B-3
12134	hydrochlorothiazide	B-3
12135	inbesartan	B-3
12136	isradipine	B-3
12137	labetalol	B-3
12138	lisinopril	B-3
12139	losartan	B-3
12140	methyldopa	B-3
12141	methyldopate	B-3
12142	metoprolol	B-3
12143	minoxidil	B-3
12144	moexipril	B-3
12145	nicardipine	B-3
12146	nifedipine	B-3
12147	nimodipine	B-3
12148	nitroprusside	B-3
12149	perindopril erbumine	B-3
12150	phenoxybenzamine	B-3
12151	phentolamine	B-3
12152	polythiazide	B-3
12153	prazosin	B-3
12154	propranolol	B-3
12155	quinapril	B-3
12156	ramipril	B-3
12157	reserpine	B-3
12158	spironolactone	B-3
12159	terazosin	B-3
12160	trandolapril	B-3
12161	triameterene	B-3
12162	trimethaphan	B-3
12163	valsartan	B-3
12164	verapamil	B-3
12165	amiloride	B-4
12166	amlodipine	B-4
12167	benazepril	B-4
12168	bumetanide	B-4
12169	candesartan cilexetil	B-4
12170	captopril	B-4
12171	carvedilol	B-4
12172	chlorothiazide	B-4
12173	chlorthalidone	B-4
12174	clonidine	B-4
12175	delodipine	B-4
12176	diazoxide	B-4
12177	diltiazem	B-4
12178	doxazosin	B-4
12179	enalapril	B-4
12180	eplerenone	B-4

12181	ethacrynic acid	B-4
12182	fosinopril	B-4
12183	furosemide	B-4
12184	guanabenz	B-4
12185	guanadrel	B-4
12186	guanethidine	B-4
12187	guanfacine	B-4
12188	hydralazine	B-4
12189	hydrochlorothiazide	B-4
12190	inbesartan	B-4
12191	isradipine	B-4
12192	labetalol	B-4
12193	lisinopril	B-4
12194	losartan	B-4
12195	methyldopa	B-4
12196	methyldopate	B-4
12197	metoprolol	B-4
12198	minoxidil	B-4
12199	moexipril	B-4
12200	nicardipine	B-4
12201	nifedipine	B-4
12202	nimodipine	B-4
12203	nitroprusside	B-4
12204	perindopril erbumine	B-4
12205	phenoxybenzamine	B-4
12206	phentolamine	B-4
12207	polythiazide	B-4
12208	prazosin	B-4
12209	propranolol	B-4
12210	quinapril	B-4
12211	ramipril	B-4
12212	reserpine	B-4
12213	spironolactone	B-4
12214	terazosin	B-4
12215	trandolapril	B-4
12216	triameterene	B-4
12217	trimethaphan	B-4
12218	valsartan	B-4
12219	verapamil	B-4
12220	amiloride	B-5
12221	amlodipine	B-5
12222	benazepril	B-5
12223	bumetanide	B-5
12224	candesartan cilexetil	B-5
12225	captopril	B-5
12226	carvedilol	B-5
12227	chlorothiazide	B-5
12228	chlorthalidone	B-5

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12229	clonidine	B-5
12230	delodipine	B-5
12231	diazoxide	B-5
12232	diltiazem	B-5
12233	doxazosin	B-5
12234	enalapril	B-5
12235	eplerenone	B-5
12236	ethacrynic acid	B-5
12237	fosinopril	B-5
12238	furosemide	B-5
12239	guanabenz	B-5
12240	guanadrel	B-5
12241	guanethidine	B-5
12242	guanfacine	B-5
12243	hydralazine	B-5
12244	hydrochlorothiazide	B-5
12245	inbesartan	B-5
12246	isradipine	B-5
12247	labetalol	B-5
12248	lisinopril	B-5
12249	losartan	B-5
12250	methyldopa	B-5
12251	methyldopate	B-5
12252	metoprolol	B-5
12253	minoxidil	B-5
12254	moexipril	B-5
12255	nicardipine	B-5
12256	nifedipine	B-5
12257	nimodipine	B-5
12258	nitroprusside	B-5
12259	perindopril erbumine	B-5
12260	phenoxybenzamine	B-5
12261	phentolamine	B-5
12262	polythiazide	B-5
12263	prazosin	B-5
12264	propranolol	B-5
12265	quinapril	B-5
12266	ramipril	B-5
12267	reserpine	B-5
12268	spironolactone	B-5
12269	terazosin	B-5
12270	trandolapril	B-5
12271	triameterene	B-5
12272	trimethaphan	B-5
12273	valsartan	B-5
12274	verapamil	B-5
12275	amiloride	B-6
12276	amlodipine	B-6

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12277	benazepril	B-6
12278	bumetanide	B-6
12279	candesartan cilexetil	B-6
12280	captopril	B-6
12281	carvedilol	B-6
12282	chlorothiazide	B-6
12283	chlorthalidone	B-6
12284	clonidine	B-6
12285	delodipine	B-6
12286	diazoxide	B-6
12287	diltiazem	B-6
12288	doxazosin	B-6
12289	enalapril	B-6
12290	eplerenone	B-6
12291	ethacrynic acid	B-6
12292	fosinopril	B-6
12293	furosemide	B-6
12294	guanabenz	B-6
12295	guanadrel	B-6
12296	guanethidine	B-6
12297	guanfacine	B-6
12298	hydralazine	B-6
12299	hydrochlorothiazide	B-6
12300	inbesartan	B-6
12301	isradipine	B-6
12302	labetalol	B-6
12303	lisinopril	B-6
12304	losartan	B-6
12305	methyldopa	B-6
12306	methyldopate	B-6
12307	metoprolol	B-6
12308	minoxidil	B-6
12309	moexipril	B-6
12310	nicardipine	B-6
12311	nifedipine	B-6
12312	nimodipine	B-6
12313	nitroprusside	B-6
12314	perindopril erbumine	B-6
12315	phenoxybenzamine	B-6
12316	phentolamine	B-6
12317	polythiazide	B-6
12318	prazosin	B-6
12319	propranolol	B-6
12320	quinapril	B-6
12321	ramipril	B-6
12322	reserpine	B-6
12323	spironolactone	B-6
12324	terazosin	B-6

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12325	trandolapril	B-6
12326	triameterene	B-6
12327	trimethaphan	B-6
12328	valsartan	B-6
12329	verapamil	B-6
12330	amiloride	B-7
12331	amlodipine	B-7
12332	benazepril	B-7
12333	bumetanide	B-7
12334	candesartan cilexetil	B-7
12335	captopril	B-7
12336	carvedilol	B-7
12337	chlorothiazide	B-7
12338	chlorthalidone	B-7
12339	clonidine	B-7
12340	delodipine	B-7
12341	diazoxide	B-7
12342	diltiazem	B-7
12343	doxazosin	B-7
12344	enalapril	B-7
12345	eplerenone	B-7
12346	ethacrynic acid	B-7
12347	fosinopril	B-7
12348	furosemide	B-7
12349	guanabenz	B-7
12350	guanadrel	B-7
12351	guanethidine	B-7
12352	guanfacine	B-7
12353	hydralazine	B-7
12354	hydrochlorothiazide	B-7
12355	inbesartan	B-7
12356	isradipine	B-7
12357	labetalol	B-7
12358	lisinopril	B-7
12359	losartan	B-7
12360	methyldopa	B-7
12361	methyldopate	B-7
12362	metoprolol	B-7
12363	minoxidil	B-7
12364	moexipril	B-7
12365	nicardipine	B-7
12366	nifedipine	B-7
12367	nimodipine	B-7
12368	nitroprusside	B-7
12369	perindopril erbumine	B-7
12370	phenoxybenzamine	B-7
12371	phentolamine	B-7
12372	polythiazide	B-7

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12374	propranolol	B-7
12375	quinapril	B-7
12376	ramipril	B-7
12377	reserpine	B-7
12378	spironolactone	B-7
12379	terazosin	B-7
12380	trandolapril	B-7
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12382	trimethaphan	B-7
12383	valsartan	B-7
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12468	lisinopril	B-9

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12515	guanadrel	B-10
12516	guanethidine	B-10

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12612	chlorothiazide	B-12

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12627	guanfacine	B-12
12628	hydralazine	B-12
12629	hydrochlorothiazide	B-12
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12632	labetalol	B-12
12633	lisinopril	B-12
12634	losartan	B-12
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12659	verapamil	B-12
12660	amiloride	B-13

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12673	doxazosin	B-13
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12708	spironolactone	B-13

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12728	doxazosin	B-14
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12756	phentolamine	B-14

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12783	doxazosin	B-15
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12803	minoxidil	B-15
12804	moexipril	B-15

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12812	polythiazide	B-15
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12814	propranolol	B-15
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12816	ramipril	B-15
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12849	hydrochlorothiazide	B-16
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12851	isradipine	B-16
12852	labetalol	B-16

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12900	guanadrel	B-17

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12957	guanfacine	B-18
12958	hydralazine	B-18
12959	hydrochlorothiazide	B-18
12960	inbesartan	B-18
12961	isradipine	B-18
12962	labetalol	B-18
12963	lisinopril	B-18
12964	losartan	B-18
12965	methyldopa	B-18
12966	methyldopate	B-18
12967	metoprolol	B-18
12968	minoxidil	B-18
12969	moexipril	B-18
12970	nicardipine	B-18
12971	nifedipine	B-18
12972	nimodipine	B-18
12973	nitroprusside	B-18
12974	perindopril erbumine	B-18
12975	phenoxybenzamine	B-18
12976	phentolamine	B-18
12977	polythiazide	B-18
12978	prazosin	B-18
12979	propranolol	B-18
12980	quinapril	B-18
12981	ramipril	B-18
12982	reserpine	B-18
12983	spironolactone	B-18
12984	terazosin	B-18
12985	trandolapril	B-18
12986	triameterene	B-18
12987	trimethaphan	B-18
12988	valsartan	B-18
12989	verapamil	B-18
12990	amiloride	B-19
12991	amlodipine	B-19
12992	benazepril	B-19
12993	bumetanide	B-19
12994	candesartan cilexetil	B-19
12995	captopril	B-19
12996	carvedilol	B-19

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12997	chlorothiazide	B-19
12998	chlorthalidone	B-19
12999	clonidine	B-19
13000	delodipine	B-19
13001	diazoxide	B-19
13002	diltiazem	B-19
13003	doxazosin	B-19
13004	enalapril	B-19
13005	eplerenone	B-19
13006	ethacrynic acid	B-19
13007	fosinopril	B-19
13008	furosemide	B-19
13009	guanabenz	B-19
13010	guanadrel	B-19
13011	guanethidine	B-19
13012	guanfacine	B-19
13013	hydralazine	B-19
13014	hydrochlorothiazide	B-19
13015	inbesartan	B-19
13016	isradipine	B-19
13017	labetalol	B-19
13018	lisinopril	B-19
13019	losartan	B-19
13020	methyldopa	B-19
13021	methyldopate	B-19
13022	metoprolol	B-19
13023	minoxidil	B-19
13024	moexipril	B-19
13025	nicardipine	B-19
13026	nifedipine	B-19
13027	nimodipine	B-19
13028	nitroprusside	B-19
13029	perindopril erbumine	B-19
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13032	polythiazide	B-19
13033	prazosin	B-19
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13041	triameterene	B-19
13042	trimethaphan	B-19
13043	valsartan	B-19
13044	verapamil	B-19

(27)

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13048	bumetanide	B-20
13049	candesartan cilexetil	B-20
13050	captopril	B-20
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13053	chlorthalidone	B-20
13054	clonidine	B-20
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13058	doxazosin	B-20
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13060	eplerenone	B-20
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13065	guanadrel	B-20
13066	guanethidine	B-20
13067	guanfacine	B-20
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13069	hydrochlorothiazide	B-20
13070	inbesartan	B-20
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13072	labetalol	B-20
13073	lisinopril	B-20
13074	losartan	B-20
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13088	prazosin	B-20
13089	propranolol	B-20
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13092	reserpine	B-20

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13108	chlorthalidone	B-21
13109	clonidine	B-21
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13112	diltiazem	B-21
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13115	eplerenone	B-21
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13117	fosinopril	B-21
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13120	guanadrel	B-21
13121	guanethidine	B-21
13122	guanfacine	B-21
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13124	hydrochlorothiazide	B-21
13125	inbesartan	B-21
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13160	captopril	B-22
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13163	chlorthalidone	B-22
13164	clonidine	B-22
13165	delodipine	B-22
13166	diazoxide	B-22
13167	diltiazem	B-22
13168	doxazosin	B-22
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13170	epplerenone	B-22
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13175	guanadrel	B-22
13176	guanethidine	B-22
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13180	inbesartan	B-22
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13182	labetalol	B-22
13183	lisinopril	B-22
13184	losartan	B-22
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13186	methyldopate	B-22
13187	metoprolol	B-22
13188	minoxidil	B-22

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13192	nimodipine	B-22
13193	nitroprusside	B-22
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13207	trimethaphan	B-22
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13209	verapamil	B-22
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13215	captopril	B-23
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13218	chlorthalidone	B-23
13219	clonidine	B-23
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13221	diazoxide	B-23
13222	diltiazem	B-23
13223	doxazosin	B-23
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13225	eplerenone	B-23
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13227	fosinopril	B-23
13228	furosemide	B-23
13229	guanabenz	B-23
13230	guanadrel	B-23
13231	guanethidine	B-23
13232	guanfacine	B-23
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13234	hydrochlorothiazide	B-23
13235	inbesartan	B-23
13236	isradipine	B-23

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13238	lisinopril	B-23
13239	losartan	B-23
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13241	methyldopate	B-23
13242	metoprolol	B-23
13243	minoxidil	B-23
13244	moexipril	B-23
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13247	nimodipine	B-23
13248	nitroprusside	B-23
13249	perindopril erbumine	B-23
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13251	phentolamine	B-23
13252	polythiazide	B-23
13253	prazosin	B-23
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13256	ramipril	B-23
13257	reserpine	B-23
13258	spironolactone	B-23
13259	terazosin	B-23
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13261	triarterene	B-23
13262	trimethaphan	B-23
13263	valsartan	B-23
13264	verapamil	B-23
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13266	amlodipine	B-24
13267	benazepril	B-24
13268	bumetanide	B-24
13269	candesartan cilexetil	B-24
13270	captopril	B-24
13271	carvedilol	B-24
13272	chlorothiazide	B-24
13273	chlorthalidone	B-24
13274	clonidine	B-24
13275	delodipine	B-24
13276	diazoxide	B-24
13277	diltiazem	B-24
13278	doxazosin	B-24
13279	enalapril	B-24
13280	eplerenone	B-24
13281	ethacrynic acid	B-24
13282	fosinopril	B-24
13283	furosemide	B-24
13284	guanabenz	B-24

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13285	guanadrel	B-24
13286	guanethidine	B-24
13287	guanfacine	B-24
13288	hydralazine	B-24
13289	hydrochlorothiazide	B-24
13290	inbesartan	B-24
13291	isradipine	B-24
13292	labetalol	B-24
13293	lisinopril	B-24
13294	losartan	B-24
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13296	methyldopate	B-24
13297	metoprolol	B-24
13298	minoxidil	B-24
13299	moexipril	B-24
13300	nicardipine	B-24
13301	nifedipine	B-24
13302	nimodipine	B-24
13303	nitroprusside	B-24
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13306	phentolamine	B-24
13307	polythiazide	B-24
13308	prazosin	B-24
13309	propranolol	B-24
13310	quinapril	B-24
13311	ramipril	B-24
13312	reserpine	B-24
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13314	terazosin	B-24
13315	trandolapril	B-24
13316	triameterene	B-24
13317	trimethaphan	B-24
13318	valsartan	B-24
13319	verapamil	B-24
13320	amiloride	B-25
13321	amlodipine	B-25
13322	benazepril	B-25
13323	bumetanide	B-25
13324	candesartan cilexetil	B-25
13325	captopril	B-25
13326	carvedilol	B-25
13327	chlorothiazide	B-25
13328	chlorthalidone	B-25
13329	clonidine	B-25
13330	delodipine	B-25
13331	diazoxide	B-25
13332	diltiazem	B-25

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13333	doxazosin	B-25
13334	enalapril	B-25
13335	eplerenone	B-25
13336	ethacrynic acid	B-25
13337	fosinopril	B-25
13338	furosemide	B-25
13339	guanabenz	B-25
13340	guanadrel	B-25
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13342	guanfacine	B-25
13343	hydralazine	B-25
13344	hydrochlorothiazide	B-25
13345	inbesartan	B-25
13346	isradipine	B-25
13347	labetalol	B-25
13348	lisinopril	B-25
13349	losartan	B-25
13350	methyldopa	B-25
13351	methyldopate	B-25
13352	metoprolol	B-25
13353	minoxidil	B-25
13354	moexipril	B-25
13355	nicardipine	B-25
13356	nifedipine	B-25
13357	nimodipine	B-25
13358	nitroprusside	B-25
13359	perindopril erbumine	B-25
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13361	phentolamine	B-25
13362	polythiazide	B-25
13363	prazosin	B-25
13364	propranolol	B-25
13365	quinapril	B-25
13366	ramipril	B-25
13367	reserpine	B-25
13368	spironolactone	B-25
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13370	trandolapril	B-25
13371	triameterene	B-25
13372	trimethaphan	B-25
13373	valsartan	B-25
13374	verapamil	B-25
13375	amiloride	B-26
13376	amlodipine	B-26
13377	benazepril	B-26
13378	bumetanide	B-26
13379	candesartan cilexetil	B-26
13380	captopril	B-26

13381	carvedilol	B-26
13382	chlorothiazide	B-26
13383	chlorthalidone	B-26
13384	clonidine	B-26
13385	delodipine	B-26
13386	diazoxide	B-26
13387	diltiazem	B-26
13388	doxazosin	B-26
13389	enalapril	B-26
13390	eplerenone	B-26
13391	ethacrynic acid	B-26
13392	fosinopril	B-26
13393	furosemide	B-26
13394	guanabenz	B-26
13395	guanadrel	B-26
13396	guanethidine	B-26
13397	guanfacine	B-26
13398	hydralazine	B-26
13399	hydrochlorothiazide	B-26
13400	inbesartan	B-26
13401	isradipine	B-26
13402	labetalol	B-26
13403	lisinopril	B-26
13404	losartan	B-26
13405	methyldopa	B-26
13406	methyldopate	B-26
13407	metoprolol	B-26
13408	minoxidil	B-26
13409	moexipril	B-26
13410	nicardipine	B-26
13411	nifedipine	B-26
13412	nimodipine	B-26
13413	nitroprusside	B-26
13414	perindopril erbumine	B-26
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13416	phentolamine	B-26
13417	polythiazide	B-26
13418	prazosin	B-26
13419	propranolol	B-26
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13421	ramipril	B-26
13422	reserpine	B-26
13423	spironolactone	B-26
13424	terazosin	B-26
13425	trandolapril	B-26
13426	triameterene	B-26
13427	trimethaphan	B-26
13428	valsartan	B-26

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13429	verapamil	B-26
13430	amiloride	B-27
13431	amlodipine	B-27
13432	benazepril	B-27
13433	bumetanide	B-27
13434	candesartan cilexetil	B-27
13435	captopril	B-27
13436	carvedilol	B-27
13437	chlorothiazide	B-27
13438	chlorthalidone	B-27
13439	clonidine	B-27
13440	delodipine	B-27
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13442	diltiazem	B-27
13443	doxazosin	B-27
13444	enalapril	B-27
13445	eplerenone	B-27
13446	ethacrynic acid	B-27
13447	fosinopril	B-27
13448	furosemide	B-27
13449	guanabenz	B-27
13450	guanadrel	B-27
13451	guanethidine	B-27
13452	guanfacine	B-27
13453	hydralazine	B-27
13454	hydrochlorothiazide	B-27
13455	inbesartan	B-27
13456	isradipine	B-27
13457	labetalol	B-27
13458	lisinopril	B-27
13459	losartan	B-27
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13461	methyldopate	B-27
13462	metoprolol	B-27
13463	minoxidil	B-27
13464	moexipril	B-27
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13466	nifedipine	B-27
13467	nimodipine	B-27
13468	nitroprusside	B-27
13469	perindopril erbumine	B-27
13470	phenoxybenzamine	B-27
13471	phentolamine	B-27
13472	polythiazide	B-27
13473	prazosin	B-27
13474	propranolol	B-27
13475	quinapril	B-27
13476	ramipril	B-27

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13477	reserpine	B-27
13478	spironolactone	B-27
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13480	trandolapril	B-27
13481	triameterene	B-27
13482	trimethaphan	B-27
13483	valsartan	B-27
13484	verapamil	B-27
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13486	amlodipine	B-28
13487	benazepril	B-28
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13490	captopril	B-28
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13493	chlorthalidone	B-28
13494	clonidine	B-28
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13497	diltiazem	B-28
13498	doxazosin	B-28
13499	enalapril	B-28
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13501	ethacrynic acid	B-28
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13503	furosemide	B-28
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13505	guanadrel	B-28
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13511	isradipine	B-28
13512	labetalol	B-28
13513	lisinopril	B-28
13514	losartan	B-28
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13516	methyldopate	B-28
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13521	nifedipine	B-28
13522	nimodipine	B-28
13523	nitroprusside	B-28
13524	perindopril erbumine	B-28

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13526	phentolamine	B-28
13527	polythiazide	B-28
13528	prazosin	B-28
13529	propranolol	B-28
13530	quinapril	B-28
13531	ramipril	B-28
13532	reserpine	B-28
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13536	triameterene	B-28
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13539	verapamil	B-28
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13541	amlodipine	B-29
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13545	captopril	B-29
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13547	chlorothiazide	B-29
13548	chlorthalidone	B-29
13549	clonidine	B-29
13550	delodipine	B-29
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13552	diltiazem	B-29
13553	doxazosin	B-29
13554	enalapril	B-29
13555	eplerenone	B-29
13556	ethacrynic acid	B-29
13557	fosinopril	B-29
13558	furosemide	B-29
13559	guanabenz	B-29
13560	guanadrel	B-29
13561	guanethidine	B-29
13562	guanfacine	B-29
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13564	hydrochlorothiazide	B-29
13565	inbesartan	B-29
13566	isradipine	B-29
13567	labetalol	B-29
13568	lisinopril	B-29
13569	losartan	B-29
13570	methyldopa	B-29
13571	methyldopate	B-29
13572	metoprolol	B-29